Quality assurance in breast cancer care and breast implant surgery

Pauline Elisabeth Richard Spronk

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Pauline Elisabeth Richard Spronk
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Promotor

Prof. R.A.E.M. Tollenaar (LUMC Leiden)

Co-promotores

Dr. C.H. Smorenburg (NKI-AVL Amsterdam)

Dr. M.T.F.D. Vrancken-Peeters (NKI-AVL Amsterdam)

Leescommissie

Prof. Dr. E. van der Wall (UMC Utrecht)

Prof. Dr. Ir. J.J.M. van der Hoeven (Radboud UMC Nijmegen)

Dr. G.J. Liefers (LUMC Leiden)

Dr. H.A. Rakhorst (MST Enschede)

Voor Wiechert

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CHAPTER 1

Introduction and outline of this thesis

INTRODUCTION

This thesis focuses on the efforts made in improving quality and patient safety of breast cancer care and breast implant surgery in the Netherlands.

In the last decades, transparency in the quality of health care has received considerable attention. Rapid innovations, growing medical costs, and patients' increasing expectations require insight into what represents 'quality of care'. Before registry of quality of health care can begin we must decide how the quality of care is to be defined. There are multiple conceptualizations of 'quality of care', based on agreed standards (norms and values) and components (the possibilities). As proposed by the Institute of Medicine (IOM): *"Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge. The identified components of quality care are: quality care is safe, effective, patient-centered, timely, efficient, and equitable"*.[1]

Aiming at measuring quality, Donabedian described health care as a function of three components which are closely related to each other: structure, process, and outcome.[2,3] Ideally, a standardized process makes the quality of care more measurable, enhances the quality of care and improves patient safety, and may eventually reduce costs. To gain insight into the quality of care, collecting data from different sources is fundamental.

Multiple national and international initiatives on quality improvement have been developed to identify a set of priority conditions upon which to focus efforts; to re-evaluate clinical practice, to facilitate benchmarking between hospitals and to ensure patients' safety. With Sweden as a pioneer, several nation-wide clinical quality registries have been initiated in the Western world, leading to demonstrable improvement in clinical outcomes and reduced variation between providers.[4,5] In the current time frame of shared-decision making, patient advocacy groups encourage the professionals to use this data in daily clinical practice. Moreover, clinical quality registries are increasingly appreciated as a source of information for research on evidence-based medicine as they provide 'real world' data on patients often not eligible for clinical trials.[6]

However, funding and sustainability of registries are highly dependent on a collaborative working relationship and culture of transparency between payers, providers, patient advocacy groups and professional medical societies. Where Sweden has succeeded, many others have found it difficult to cultivate an environment in which stakeholders join forces in such harmony. In 2011, the Dutch Institute of Clinical Auditing (DICA) was founded, with the objective to facilitate and organize the start-up of new nation-wide audits in the Netherlands.[7] One of the key factors of success of DICA is the leading role of clinicians and professional medical societies in defining and agreeing on outcome data sets. This approach guarantees clinician commitment and ownership, resulting in high participation rates, high-quality data in the registry, and the completion of quality improvement loops. Funding is achieved by several large stakeholders, aiming for independence, consisting of the Dutch Ministry of Health and Health Insurance Companies.[8]

DICA's primary aim is to drive positive results in both health care outcome and costs. The results of the Dutch Surgical Colorectal Audit (DSCA) showed that substantial clinical improvements can be realized within a short period of time.[4] For example, there was a reduction in surgical complications from 33% to 30% for colon cancer, and 40% to 37% for rectal cancer from 2009 to 2011 (and further continued). Subsequent to the success of the DSCA, at present twenty-two national registries covering a wide range of medical conditions have been established in the Netherlands, including the National Breast Cancer Audit (NBCA) and the Dutch breast implant registration (DBIR).

With the foundation of the NBCA and the DBIR, interesting data became available on breast cancer diagnosis and therapy (NBCA), and on breast implant surgery (DBIR). In **part 1** of this thesis, we discuss some important trends in breast cancer treatment in the Netherlands, e.g. the actual use of neoadjuvant chemotherapy (NAC), breast-conserving therapy and axillary lymph-node management. In **part 2** of this thesis, we illustrate key elements of the DBIR and the first results of two years of registration.

I. Quality assurance in breast cancer care

Breast cancer is the most common female affecting cancer type worldwide.[9] In the Netherlands over 15.000 women get diagnosed with breast cancer every year.[10] Until recently, the quality of breast cancer care was mainly directed by the National Breast

Cancer Organisation Netherlands (NABON) that defined and distributed guidelines that contained multidisciplinary criteria for providing good breast cancer care.[11] In 2008, the Dutch Health Care Institute published a report regarding the large differences between what is considered standard of care and what people actually received in different hospitals in the Netherlands. For example, there was a large difference between hospitals in their rate of tumor involved margins after breast-conserving therapy. With the purpose to monitor and improve the quality of breast cancer care in the Netherlands, the NABON Breast Cancer Audit (NBCA) was instituted as a nation-wide audit in 2011. All patients who are surgically treated for newly diagnosed breast cancer in the Netherlands are registered (since 2011), and information on diagnostic and treatment modalities are structured. The main purpose of the NBCA was to provide health care providers with reliable, benchmarked information on structure, process and outcome parameters that can be used to improve quality of care and can be used for shared-decision making in clinical practice. A multidisciplinary set of quality indicators was defined as a means of quality assurance.

In one of the first reports based on NBCA data, van Bommel et al. described the results of 4 years of auditing.[12] The use of quality indicators, embedded in a national audit providing benchmark information, has led to significant improvements on hospital level. Hospitals recognized themselves as being an 'outlier' on certain indicators, evaluated their processes and found keystones for improvement (e.g. adjustments in reporting results, other ways of organizing Multidisciplinary Team Meetings (MDTs) and new partnerships between hospitals were initiated). Apart from the actions of the individual hospitals, work has been established to synthesize, implement and monitor 'best practice'. The comprehensive audit outcomes enabled research into hospital variation associated with the adoption of several monitor and treatment modalities.[13,14,15,16]

Neoadjuvant chemotherapy

Breast cancer (BC) care consists of a multidisciplinary approach of surgery, radiation, and systemic therapy including chemotherapy.[11] Chemotherapy can be timed either prior to or following surgery; so-called neoadjuvant (NAC) or adjuvant (AC) chemotherapy. Initially, NAC was used exclusively in the treatment of inoperable breast cancer in order to reduce the tumor burden and allow resection with mastectomy.[17] The role of preoperative therapy broadened when the National Surgical Adjuvant Breast and

Bowel (NSABP) project B-18 trial demonstrated that patients who underwent NAC were significantly more likely to receive breast-conservation therapy than patients who were treated with AC.[18,19,20] Other potential advantages of NAC include the opportunity to investigate tumor biology, to monitor response to systemic therapy and to adapt to suboptimal response.[21] Moreover, NAC may improve survival in triple-negative and HER2 positive BC subtypes when a pathologic complete response (pCR) is achieved.[22]

In **chapter 2**, we examine the use of NAC in patients with stage III breast cancer in the Netherlands and assessed which patient, tumor and hospital-related factors influenced clinical practice. Locally advanced (or stage III breast cancer) is defined as a bulky tumor of the breast and/or extensive nodal disease. The prognosis of stage III breast cancer is still poor with a ten-year overall survival of only 56%.[10] The Dutch national breast cancer guideline recommends NAC for all patients with stage III breast cancer aged <70 years, in accordance with international guidelines.[23,24]

Because patient and disease characteristics determine possible treatment options for a specific condition, demand factors contribute to variation in care on an individual level. However, several national and international studies have shown that after case-mix adjustment considerable unexplained variation in the use of NAC remains between hospitals[13,16,25,26,27], as was indeed shown in results from chapter 2.

The preferences of both patient and clinician and the level of shared decision-making may be important factors in the decision for certain use of health care. Moreover, 'physician supply-side factors', such as clinicians' preferences, style of practice and incentives, may be even more important factors in explaining inter-hospital variations than patient demand.[28]

To gain insight in the reasons for the observed considerable variation in the use of NAC in patients with breast cancer, we have deployed further research to examine the role of patient- and specialist preferences in shared-decision making on NAC in patients with breast cancer. In **chapter 3**, we evaluate the current opinion of surgical and medical oncologists in the Netherlands on the use of NAC and their decisions towards NAC in early breast cancer. **Chapter 4** displays patients' experiences with decisions on the timing of chemotherapy for stage II and III BC.

Breast-conserving therapy

As systemic therapy becomes more effective, the use of NAC has increased, enabling more patients to potentially undergo breast-conserving therapy (BCT). There are many questions, however, that remain unanswered. While NAC has been shown to increase the rate of BCT in clinical trials[29], it is unknown how NAC is being used to improve the use of BCT in general community practice and what the surgical outcomes (including margins and re-excision rates) are for BCS after NAC compared to primary BCS. In **chapter 5** we, therefore, analyzed national trends in the use of BCS after NAC in early breast cancer and the surgical outcomes after NAC in the Netherlands.

Axillary lymph-node management

In **chapter 6**, we investigate the implementation process in the Netherlands of omitting ALND in cT1-2N0M0 sentinel node-positive breast cancer patients after the publication of the ACOSOG-Z0011 and AMAROS trial. Previously, performing an axillary lymph node dissection (ALND) was the standard of care for all non-metastatic breast cancer patients. However, this treatment is associated with significant long-term problems such as pain, arm swelling (lymphedema), restricted shoulder movement, and sensory changes in the arm and hand.[30,31] In the early nineties, sentinel lymph node biopsy (SLNB) was introduced as an accurate and less invasive axillary staging procedure, omitting the need for an axillary lymph node dissection in cT1-2N0M0 sentinel node-negative breast cancer patients.[32,33] The additional value of ALND in cT1-2N0M0 breast cancer patients with 1-2 detected *positive* sentinel lymph nodes was further questioned in two important randomized controlled trials; the ACOSOG-Z0011 trial and the AMAROS trial. The main objective of ACOSOG Z0011 was to compare locoregional recurrence-free survival for these patient population managed with or without ALND and no axillary irradiation.[34] The AMAROS trial evaluated whether regional control was comparable between ALND and axillary radiation therapy in cT1-2N0M0 breast cancer patients with a positive sentinel lymph node.[35] The results of these trials indicate that in case of a positive sentinel node, both ALND and axillary radiotherapy provide excellent and comparable axillary control in terms of disease-free and overall survival. This is illustrated by the 2012 Dutch breast cancer guideline, suggesting omission of ALND in cT1-2N0 breast cancer patients with a maximum of two positive sentinel nodes treated with breast-conserving treatment and adjuvant systemic therapy.

II. Quality assurance in breast implant surgery

Breast implants are used routinely for purposes of breast reconstruction and breast augmentation. Since the introduction five decades ago, problems with a variety of breast implants have emerged with direct consequences for the patients' health. Plastic surgeons worldwide reacted through campaigning for auditing on long-term implant quality, surgeon performance and institutional outcomes in implant registries. Especially, the Poly Implant Prothèse (PIP) crisis[36,37] and more recent reports on breast implant-associated anaplastic large cell lymphoma[38,39] have raised awareness of the need for long-term follow-up and clinical registries for long-term safety reasons. Various reports e.g. by the European Union, the FDA and other stakeholders, stress the importance of a well-organized clinical registry including epidemiological data to assess the appropriateness and effectiveness of a specified clinical issue, whether it is an implantable device or care pathway.[40]

The Dutch Breast Implant Registry (DBIR)

In the Netherlands, an estimated 30.000 implants are inserted annually. As an initiative of the Association of Plastic Surgeons of the Netherlands (NVPC), the Dutch Breast Implants Registry (DBIR) was instituted in April 2015, as a nation-wide audit to monitor breast implant quality and complications, independently from the industry. The main purpose of the DBIR is to enable benchmarking between hospitals and surgeons and to develop a 'track-and-trace system' with the implants and patients. Since the start of the DBIR in April 2015, all board-certified plastic surgeons are required to register their implants in the system and thousands of implants have been registered. Since 2016 registry of all sorts of medical implants is being required by the Dutch Health Inspectorate.

The dataset of the DBIR is based on the dataset constructed by the international Collaboration of Breast Registry Activities (ICOBRA).[41] Patient data including indication for surgery, unique and descriptional implant data, operation details and data regarding surgical technique. Also, the reasons for revision or explantations are collected. **Chapter 7** gives an overview of which numbers and types of implants, patients and interventions have been registered in the Netherlands since April 2015.

The International Collaboration of Breast Registry Activities (ICOBRA)

In 2012, the International Collaboration of Breast Registry Activities (ICOBRA) was founded by the Australian Society of Plastic Surgeons to improve breast device registries by sharing datasets and connecting organizations from various countries all over the world.[41] The members of ICOBRA include national plastic surgery societies or multidisciplinary breast implant registries of several countries, including Australia, Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, the United Kingdom, and the United States. Each country has an independent registry, but all are using largely similar datasets. Harmonization of data points and data definitions is key in order to compare and pool data from registries. Pooling is crucial to amplify the data and reduce the time needed to identify implants performing well and those associated with higher rates of adverse events, such as anaplastic lymphoma or capsular contraction. We, therefore, set out to identify and define an internationally agreed minimum core set of data points to be used by all breast device registries globally (**chapter 8**).

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CHAPTER 2

Variation in use of neoadjuvant chemotherapy in patients with stage III breast cancer: results of the Dutch national breast cancer audit

P.E.R. Spronk
A.C.M. van Bommel
S. Siesling
M.W.J.M. Wouters
M.T.F.D. Vrancken Peeters
C.H. Smorenburg

The Breast 2017;36:34-38

ABSTRACT

Objective: Neoadjuvant chemotherapy (NAC) is important in the optimal treatment of patients with locally advanced (stage III) breast cancer (BC). The objective of this study was to examine the clinical practice of NAC for stage III BC patients in all Dutch hospitals participating in BC care.

Materials and methods: All patients aged 18-70 years who received surgery for stage III BC from January 2011 to September 2015 were selected from the national multidisciplinary NABON Breast Cancer Audit. Multivariable logistic regression was used to assess independent predictors of NAC use, focusing on hospital factors.

Results: A total of 1230 out of 1556 patients with stage III BC (79%) received NAC prior to surgery. The use of NAC did not change over time. We observed a large variation of NAC use between hospitals (0-100%). Age <50 years, breast MRI, large tumour size, advanced nodal disease, negative hormone receptor status and hospital participation in neoadjuvant clinical studies were significant independent predictors of NAC use (all $P<0.001$). NAC use in stage III BC was not influenced by hospital type and hospital surgical volume. After adjustment for all independent predictors, variation in NAC use between hospitals remained (0% to 97%).

Conclusion: NAC was used in 79% of patients with stage III BC, which represent a high quality of care in the NL. Patient, tumour, clinical management and hospital factors could not explain considerable variation in its use between hospitals. Hospital participation in neoadjuvant studies did show to improve the use of NAC in daily practice.

INTRODUCTION

Locally advanced or stage III breast cancer (BC) is defined as a bulky tumour of the breast and/or extensive nodal disease. The prognosis of stage III BC is worse than early stage disease showing a ten-year overall survival in only 56% of patients[1]. As multimodality treatment improves the outcome of Stage III BC, neoadjuvant chemotherapy (NAC) has become an important initial treatment strategy. NAC aims to downsize the tumour to improve the possibility of a radical resection or even to enable breast conserving surgery[2-4]. Other potential advantages of NAC include the opportunity to investigate tumour biology, to monitor response and adapt to suboptimal response. Several studies have demonstrated that NAC, when compared to adjuvant chemotherapy, leads to similar overall and disease-free survival and may even improve survival in triple-negative and HER2 positive BC subtypes when pCR is achieved[5-8]. In accordance with international guidelines[10-11], the Dutch national breast cancer guideline recommends NAC for patients with stage III BC aged <70 years[12].

The NABON Breast Cancer Audit (NBCA) is a multidisciplinary nationwide registry of all diagnostic and treatment modalities of patients who are surgically treated for BC in the Netherlands since 2011. This audit provides the opportunity to gain insight into patterns of practice in different hospitals by creating a national benchmark. Knowledge of variation in the use of NAC for stage III BC and the reasons for this variation may help in bringing down barriers to use upfront chemotherapy and to improve outcome in these patients. The objective of the present study was therefore to examine the use of NAC in patients with stage III BC in the Netherlands and to assess which patient, tumour and hospital related factors influence clinical practice.

METHODS

The NBCA is a nationwide registry that captures 100% of all newly diagnosed and surgically treated breast cancer patients in the Netherlands. We selected data from the NBCA database on all patients aged 18-70 years diagnosed with stage III BC (clinical cT1-4N2, cT3N1-3, cT4N0, M0) from January 2011 to September 2015. In the given time frame, 63.315 patients with invasive breast cancer are registered in the NBCA, which means a proportion of 2,46% stage III patients aged 18-70 years. Tumour stage was defined according to the 7th edition of the International Union Against Cancer tumour node metastasis (TNM) classification[13]. We excluded patients with a prior cancer diagnosis or unknown sequence of chemotherapy and surgery. Patients aged 70 years and older were also excluded, because the use of NAC is not considered standard treatment in the elderly[12]. Patients who received both neoadjuvant- and adjuvant chemotherapy were not excluded from this study.

Construction of variables

The primary outcome of the study was the use of NAC, defined as chemotherapy given within four weeks prior to surgery, for stage III BC in the different hospitals in the Netherlands. The hospital of treatment was defined as the hospital where the first therapeutic surgical intervention was conducted. Available data from the NBCA dataset regarding the use of NAC includes factors of the patient (year of incidence, age), the tumour (histologic subtype, clinical tumour stage, clinical nodal stage and hormone receptor status), clinical management and various hospital related factors. The surgical volume of a hospital was defined as the mean annual number of breast cancer surgeries during the period 2011-2015; divided into low-volume (<150), mid-range (150-300) and high-volume (>300) categories. Type of hospital was described as academic, teaching and general hospitals. Academic hospitals are part of a university, and both academic and teaching hospitals provide medical training to surgical residents. Between 2011 and 2015, there were three clinical trials regarding neoadjuvant therapy in which participation was possible: NEO-ZOTAC, TRAIN-2 and TEAM IIa[14]. Information on tumour grade was excluded, because of missing data.

Statistical analysis

The Pearson's Chi-square test was applied to test associations of the use of NAC and the covariates in the entire study population. A multivariable logistic regression model was used to determine whether patient, tumour, clinical management and hospital factors were independent predictors associated with the odds of receiving NAC in comparison with patients who were treated only surgically with or without adjuvant therapy. The multivariable logistic regression model was used to quantify the percentage of NAC in daily practice and to reveal the variation among the 89 Dutch hospitals adjusted for the predictors[15]. Statistical significance was defined as a two-sided p value < 0.05. All analyses were performed in PASW Statistics version 20 (SPSS inc Chicago, IL, USA).

RESULTS

We identified 1556 surgically treated patients with stage III BC aged 18-70 between 2011 and 2015 in the Netherlands. A total of 1230 patients (79%) with stage III BC received NAC. The rate of NAC did not significantly change over time.

Table 1a shows the patient, tumour and clinical management factors according to the use of NAC. The median age of patients with stage III disease was 51 years (range 19-70 years). The median age of treated patients in general hospitals was 53.0 years compared to 51.4 years in teaching hospitals and 49.1 years in academic hospitals ($p < 0.001$). In case a breast MRI was performed or when the patient had been discussed in a preoperative MDT, a significantly higher rate of NAC use was observed (84% versus 57%, $p<0.001$; 79% versus 68%, $p=0.038$). Of notice, a total of 227 patients (87%) in which breast conserving surgery was performed, received NAC compared to 1003 patients (77%) in which a mastectomy was performed ($p<0.001$). Hospital factors regarding NAC use are depicted in **Table 1b**. The median number of surgically treated patients with stage III BC per hospital was 15 (range 2-99). Significant more patients in academic hospitals received NAC (88%) as compared to patients in teaching hospitals (79%) or in general hospitals (75%) ($p<0.001$). The use of NAC in hospitals participating in neoadjuvant clinical studies was significantly higher (83%) than in hospital not doing so (73%) ($p<0.001$).

Table 1A. Factors of patient, tumour and clinical management regarding the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (N=1556)

		Stage III	NAC		*P-value*
		(n)	(n)	%	
Year of incidence	2011	204	158	77%	0,283
	2012	306	244	80%	
	2013	357	271	76%	
	2014	377	299	79%	
	2015	312	258	83%	
Age	<40	162	137	85%	0,000
	40-50	547	462	84%	
	50-60	470	362	77%	
	60-70	377	269	71%	
Histologic subtype	ductal	1293	1044	81%	0,000
	lobular	263	186	71%	
Clinical tumor stage	cT1	20	7	35%	0,000
	cT2	48	31	65%	
	cT3	995	768	77%	
	cT4	493	424	86%	
Clinical nodal status	cNx/N0	116	85	73%	0,000
	cN1	1250	992	79%	
	cN2	95	64	67%	
	cN3	95	89	94%	
Hormone receptorstatus	triple -	235	200	85%	0,000
	HR- HER2+	171	152	89%	
	HR+ HER2+	214	165	77%	
	HR+ HER2-	936	713	76%	
Preoperative MDT	No	60	41	68%	0,038
	Yes	1496	1189	79%	
Breast MRI	No	284	162	57%	0,000
	Yes	1272	1068	84%	
Type of surgery	BCS	260	227	87%	0,000
	Mastectomy	1296	1003	77%	

MDT= multidisciplinary team
BCS= breast conserving surgery

To determine the independent predictors of NAC use, a multivariable logistic regression analysis was conducted (**Table 2**). Age <50 years, breast MRI, large tumour size, advanced nodal disease, negative HR status and hospital participation in neoadjuvant clinical studies remained significant (all p<0.001). Hospital type and hospital surgical volume were not independently associated with the use of NAC.

The variation between hospitals in the Netherlands in the percentage of patients with stage III BC receiving NAC during 2011-2015 is depicted in **Fig. 1**. The median is 48,3% and a large variation in its use was observed (0-100%). After adjusting for independent predictors according to our multivariable model, the rate of NAC per hospital over the period 2011-2015 were modified from minus 8,9% to plus 22%. One hospital with only two patients with stage III BC, neither of whom received NAC, accounted for the number of 0%. According to the 95% confidence interval (CI), three hospitals were negative outliers (significant lower rates than average).

Table 1B. Factors on hospital level regarding the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (N=1556)

		Hospitals	Stage III	NAC		*P-value*
		(n)	(n)	(n)	%	
Type of hospital	General	37	390	291	75%	0,001
	Teaching	43	957	755	79%	
	Academic	9	209	184	88%	
Hospital surgical	<150	44	455	348	76%	0,148
volume	150-300	34	692	547	79%	
	>300	11	409	335	82%	
PET-CT available	No	56	700	538	77%	0,055
	Yes	33	856	692	81%	
Hospital study participation	No	48	604	440	73%	0,000
	Yes	41	952	790	83%	

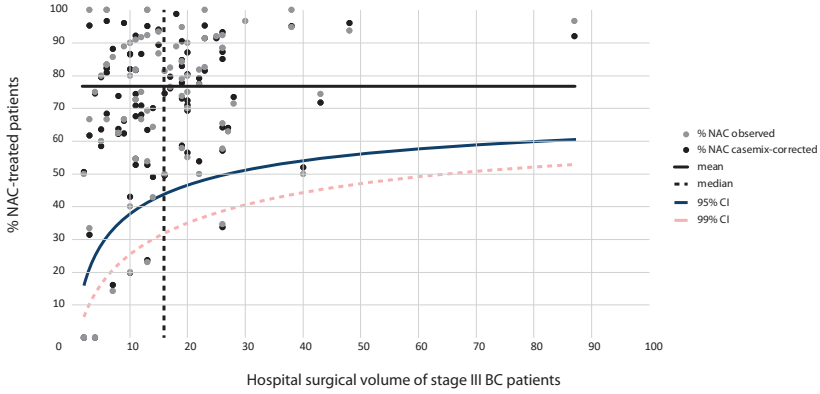

Figure 1. Variation between hospitals in the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (n=1556) in the Netherlands in 2011-2015.

Table 2. Multivariable logistic regression of the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (N=1556)

		OR	95% C.I.		*Sig.*
			Lower	Upper	
Age	<40	ref.			0,000
	40-50	1,12	0,679	1,849	
	50-60	0,677	0,41	1,118	
	60-70	0,458	0,275	0,762	
Histologic subtype	ductal	ref.			0,021
	lobular	0,674	0,482	0,942	
Clinical tumor stage	cT1	0,091	0,025	0,337	0,000
	cT2	0,228	0,078	0,664	
	cT3	ref.			
	cT4	2,46	1,653	3,662	
Clinical nodal status	cN0	0,398	0,227	0,698	0,000
	cN1	ref.	1,195	4,19	
	cN2	1,671	0,671	4,158	
	cN3	5,13	1,734	15,178	
Hormone receptorstatus	triple -	ref.			0,004
	HR -, HER2+	1,502	0,8	2,821	
	HR+, HER2-	0,675	0,445	1,025	
	HR+, HER2+	0,567	0,342	0,94	
Preoperative MDT	No	ref.			0,495
	Yes	1,927	1,043	3,559	
Type of hospital	General-	ref.			0,058
	Teaching-	1,04	0,708	1,527	
	Academic-	1,824	1,042	3,194	
Hospital surgical	<150	ref.			0,999
volume	150-300	1,01	0,674	1,515	
	>300	1,013	0,596	1,721	
PET-CT available	No	ref.			0,517
	Yes	0,881	0,6	1,293	
Study participation	No	ref.			0,000
	Yes	1,832	1,366	2,457	

MDT= multidisciplinary team

DISCUSSION

In this nationwide population-based study from 2011 to 2015 in the Netherlands, we observed that 1230 out of 1556 of women aged 18-70 years with stage III BC (79%) were treated with NAC prior to surgery. Various recent studies reveal an international trend on the increasing implementation for NAC in patients with BC. The high rate of NAC in The Netherlands did not significantly change over time. Our data compare favourably with those reported from cancer registries in other countries. For stage III BC, Mougalian et al. used data from the National Cancer Data Base of America and reported a mean use of NAC in 41.6% of 71,433 patients during 2003-2011, while they observed an increase to 59.3% in 2011[16]. Recent studies from the United States on patients with all stages of BC showed a major increase in the use of NAC during the last decade, with a proportion of 10-20% of BC patients treated with NAC[2,17]. A similar increase was seen in a population study of 10 Dutch hospitals in which the use of NAC for BC increased from 2.5% in 2003 to 13% in 2012[18]. During this time span, the use of NAC for cT3 BC increased from 30.6% to 70.9%. A French survey reported the use of NAC in 16.3% of patients with BC in 2010, but data on stage of disease were incomplete[19].

In line with other studies[16,17,20], we found the following predictive patient and tumour factors for the use of NAC in patients with BC: young age, large tumour size, advanced nodal disease and a negative hormone receptor status. Going beyond the scope of prior studies, we also assessed factors at hospital level and observed that the surgical volume and type of hospital was not independently associated with the use of NAC in the Netherlands. This has been previously observed by a study in the Netherlands on variation in adjuvant chemotherapy[19] and is presumably due to the consultancy of experts in oncology meetings between academic, teaching and general hospitals. Of notice, we observed a significantly higher use of NAC in hospitals participating in neoadjuvant clinical studies (83% versus 73%). Study participation is an instrument of cultural change. It creates more awareness among physicians and it narrows the gap between the best available evidence and current practice. Moreover, it also requires an adjustment of the current pattern of care and may facilitate the implementation of new therapeutic concepts.

Variation in the use of NAC between hospitals is in line with international literature, except that these studies did not adjust for hospital related factors and did not exclude patients >70 years of age with possible contraindications[2,16,20]. After adjustment according to our multivariable model, we observed a constant proportion of 77% and considerable variation between 89 hospitals remained.

The preferences of both patient and clinician and the level of shared decision-making may be important factors in the decision to use or to refrain from NAC. It may be possible that many women prefer to undergo surgery first because of an incorrect idea of delayed surgery or because of a preference for mastectomy (in combination with a reconstruction). Patients may not realise that neoadjuvant treatment is a viable choice. It has been demonstrated that clinicians' treatment recommendations and preferences exert one of the most powerful influences over patients' decisions[21,22].

Valid options to refrain from NAC may be a contraindication for chemotherapy such as poor performance status or severe comorbidity, or the choice for neoadjuvant hormonal therapy in lowgrade highly endocrine-sensitive BC. Other factors such as under capacity or financial incentives could negatively affect the implementation of NAC. In-hospital factors such as the level of training of physicians, the composition of MDT meetings and an integrated oncological care pathway for BC may also account for discrepancies between hospitals[23,24]. Confirmed by our univariate analyses, preoperative MDT is significantly associated with NAC use.

The main strength of the present study is the multivariable adjustment for hospital case mix, including factors regarding patient, tumour, clinical management and hospital level. Additionally, because our data covers all surgically treated BC patients in the Netherlands we can more reliable understand clinical practice. Unfortunately, we had no data available regarding the reason why NAC was omitted, such as patient performance status, comorbidities, genetic risk factors and other treatment decision-making factors.

In conclusion, our study shows that NAC is being used in 79% of patients with stage III BC, which stands for high quality of care compared to the international percentages of NAC use reported. Still, 21% of patients did not receive NAC prior to surgery. After

adjustment for all independent predictors of NAC, a considerable variation remained between hospitals. Hospital participation in neoadjuvant clinical studies may be a major factor contributing to a more rapid implementation of NAC in daily practice. We have deployed further research to examine the role of patient- and specialist preferences in shared-decision making on NAC in patients with BC.

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CHAPTER 3

Current decisions on neoadjuvant chemotherapy for early breast cancer: Experts' experiences in the Netherlands

P.E.R. Spronk
K.M. de Ligt
A.C.M. van Bommel
S. Siesling
C.H. Smorenburg
M.T.F.D. Vrancken Peeters
on behalf of the NABON Breast Cancer Audit

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ABSTRACT

Purpose: To evaluate the opinion of surgical and medical oncologists on neoadjuvant chemotherapy (NAC) for early breast cancer.

Methods: Surgical and medical oncologists (N=292) participating in breast cancer care in the Netherlands were invited for a 20-question survey on the influence of patient, disease, and management related factors on their decisions towards NAC.

Results: A total of 138 surgical and medical oncologists from 64 out of 89 different Dutch hospitals completed the survey. NAC was recommended for locally advanced breast cancer (94%) and for downstaging to enable breast conserving surgery (BCS) (75%). Despite willingness to downstage, 64% of clinicians routinely recommended NAC when systemic therapy was indicated preoperatively. Reported reasons to refrain from NAC are comorbidities (68%), age >70 years (52%), and WHO-performance status ≥2 (93%). Opinions on NAC and surgical management were inconclusive; while 75% recommends NAC to enable BCS, some stated that BCS after NAC increases the risk of a non-radical resection (21%), surgical complications (9%) and recurrence of disease (5%).

Conclusion: This article emphasizes the need for more consensus among specialists on the indications for NAC in early BC patients. Unambiguous and evidence-based treatment information could improve doctor-patient communication, supporting the patient in chemotherapy timing decision-making.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) is an important initial strategy for the management of operable breast cancer (BC). In accordance with international guidelines, the Dutch national breast cancer guideline recommends NAC as an option for all patients aged <70 with an indication for systemic treatment, as similar overall and disease-free survival rates were demonstrated between preoperative and postoperative application of chemo-therapy[1-4]. These guidelines disclose that NAC may be used for large tumours (T3; >5cm) to increase resectability and the rate of breast conserving surgery and axillary preserving surgery[5]. Besides, chemotherapy prior to breast surgery remains a valuable therapeutic approach for the assessment of biological anti-tumour activity and clinical efficacy of new treatments[6]. Furthermore, administration of NAC creates a time frame for testing on hereditary breast cancer and planning the final type of surgery, for example reconstruction surgery.

Despite these arguments in favour of NAC, large national and international variation in the application of NAC is observed between hospitals[7,8]. Previous research based on data from the NABON Breast Cancer Audit (NBCA) revealed that most variation between hospitals consists in the treatment of BC stage IIB with a national average of 40% NAC use. For BC stage III, the national average is 80%. After adjustment for patient and tumour factors associated with the use of NAC, including hospital study participation, a consider- able unaccountable variation still remained between all 89 Dutch hospitals[9,10].

Additional factors, such as clinician preferences and the level of shared decision-making, may play a role in the application of NAC[11]. Since it has been demonstrated that clinicians' treatment recommendations exert one of the most powerful influences over patients' preferences, the clinicians' opinion on NAC is therefore of great importance[12]. Some specialists adhere firmly to their personal treatment preferences which may lie outside evidence of best practice or safety[13]. Consequently, differences in surgeons and medical oncologists' opinions may lead to unwanted variation in treatment patterns. As options of chemotherapy timing are in equilibrium for overall and disease-free survival, but NAC also yields several advantages, it is important to gain insight in the

observed variation of NAC application, as each patient indicated for NAC deserves a choice in chemotherapy timing.

The aim of this study is to evaluate the current opinion of surgical and medical oncologists in the Netherlands on the use of NAC and their decisions towards NAC in early breast cancer.

METHODS

Participants

On November 11, 2015, an invitation for an online survey was sent by mail to 575 surgical and medical oncologists, invited by the network of the NABON Breast Cancer Audit (NBCA), covering all Dutch hospitals that are involved in breast cancer care. A reminder was sent to non-respondents 3 weeks later and the survey was closed on January 8th, 2016.

Demographics of participating hospitals were derived from the NBCA dataset. The surgical volume of a hospital was defined as the mean annual number of breast cancer surgeries during the period 2011–2015; divided into low-volume (<150), mid-range (150–300) and high-volume (>300) categories. Type of hospital was described as academic, teaching, and general hospitals. Academic hospitals are part of a university, and both academic and teaching hospitals provide medical training to surgical residents.

Survey

The survey was developed by a multidisciplinary taskforce, including a medical oncologist, a breast cancer surgeon, a clinical epidemiologist and medical researchers. Hereafter, the survey was pre-tested and modified based on the obtained feedback. The survey consisted of 20 questions about (contra) indications and considerations for NAC and general information about the survey participants. Part one of the survey consisted of eight questions about commonly accepted indications and contraindications of NAC on the following categories: tumour characteristics (tumour size, stage and biology), patient characteristics (age, performance status and comorbidities) and clinical disease management (genetic testing and timing of final surgery) (**supplement 1**). The 5-point Likert scale was used to allow the respondent to express how much they agree or disagree. Part two of the survey consisted of four questions about other possible considerations that could influence the use of NAC (evidence in overall and disease-free survival benefit of NAC, axillary conservation surgery, risk of complications, risk of non-radical resections), using a yes/no scale. Throughout the survey there was the ability to write and add comments in the responses. To get an idea of the level of experience per specialist, demographic data, numbers of years in specialty, numbers of patients treated, and questions on study participation were included in the survey.

Statistical analysis

Frequencies and percentages were used to display responses to individual questions. Differences between surgical and medical oncologists' responses were analysed using Pearson chi-square. Statistical significance is defined as a two-sided p value <0.05. All analyses are performed in PASW Statistics version 24 (SPSS inc Chicago, IL, USA).

RESULTS

A total of 292 clinicians opened the online program, of whom 138 clinicians from 64 out of 89 Dutch hospitals completed the survey, leading to a response rate of 473%. Of 138 respondent clinicians, 70 surgical oncologists (43% female, 57% male) and 68 medical oncologists (59% female, 41% male) participated in the survey. The respondents had been in clinical practice for a median of 12 years (range 1-35). The number of annually treated breast cancer patients varied from 50 patients for medical oncologists (range 15-110) to 70 patients for surgical oncologists (range 30-110). The majority of clinicians included more than 10 patients in neoadjuvant chemotherapy trials per year. This survey represented two-third of Dutch hospitals; 22 hospitals had only one representative and 42 hospitals were represented by 2-7 representatives. Medical oncologists and surgical oncologists were evenly represented according to type and volume of hospitals (**Table 1**).

Survey

Respondents rated locally advanced breast cancer (LABC) as the most distinguished indication for NAC (94%). The second commonly accepted indication is down staging of the tumour to enable breast conserving surgery (75%). Of all respondents, 64% "always to frequently" recommended NAC if systemic therapy is indicated preoperatively, based on known clinical tumour characteristics (**Fig. 1A**). Reported reasons to refrain from NAC were WHO-performance status ≥2 (93%), comorbidities (68%), and age >70 years (52%) (**Fig. 1C and D**).

A WHO-performance score of ≥2, which implies an inability to carry out any work activities, was reported as the most common contraindication. Age by itself was no contraindication according to 48% of respondents. But if so, patients aged <70

Table 1. Respondents' and affiliated hospital demographics.

	Surgeons (N=70)	Oncologists (N=68)	Hospitals (N=64)	*P-value*
Sex				
Male	40	28		0,106
Female	30	40		
n of yrs in practice				
<10	27	27		0,774
10 - 19	32	27		
20+	11	14		
n of patients per specialist/year				
<50	8	24		0,001
50 - 99	23	25		
100+	32	15		
n of patients per specialist included in NAC studies/year				
<10	21	12		0,001
>10	39	52		
Volume of hospital*				
<150	27	29	31	0,578
150-300	23	25	22	
>300	20	14	11	
Type of hospital*				
General-	19	22	24	0,281
Teaching hospital-	43	33	34	
Academic-	8	13	6	

*Derived from the NBCA-registry.

seemed to be the main reason for restrained application of NAC. Clinical management factors, such as the time necessary for testing on hereditary breast cancer or to plan the final type of reconstructive surgery, were less frequently denominated as indications for NAC (**Fig. 1B**).

In the second part of the survey, clinicians were asked about other considerations that could influence the use of NAC (**Table 2**). More than half of the respondents (60%), especially medical oncologist (83%), stated that the evidence in overall and disease-free survival benefits of NAC compared to adjuvant chemotherapy is not established yet (p-value: 0,015). While in the first part of the survey 75 percent of the respondents

mentioned increased breast conservation rate as an indication for NAC, a concern about non-radical resections is raised by 21% of the respondents (surgeons 292%, medical oncologists 158%, p-value: 0,078). A minor consideration in performing surgery after NAC was the increased chance of surgical complications (9%). Finally, in a relative high percentage of clinicians (63%), NAC is also being used to enable axillary conserving surgery.

In added comments, a frequently described benefit of neo-adjuvant therapy was the extra time for patient work-up for surgery, for example in case of controlling diabetes or smoking cessation. Reported barriers for recommending NAC were lack of patient cooperation, logistic challenges (for example a far travel distance to the hospital), a term pregnancy, oocyte preservation, or a patient's desire to undergo surgery first.

Table 2. Agreement with statements on NAC by responding surgeons and medical oncologists.

	YES	Surgeons (N=70)	Oncologists (N=68)	*P-value*
"NAC improves the chance of achieving axillary conservation surgery"	63%	70,8% (46)	62,9% (39)	0,346
"NAC increases the risk of surgical complications"	9%	13,3% (8)	6,9% (4)	0,247
"Breast conservation surgery after NAC increases the risk of a non-radical resection"	21%	29,2% (19)	15,8% (9)	0,078
"Breast conservation surgery after NAC increases the risk of recurrence"	5%	6,5% (4)	4,8% (3)	0,697
"There is no evidence for an overall and disease-free survival benefit of NAC compared to AC"	60%	62,3% (33)	82,8% (48)	0,015

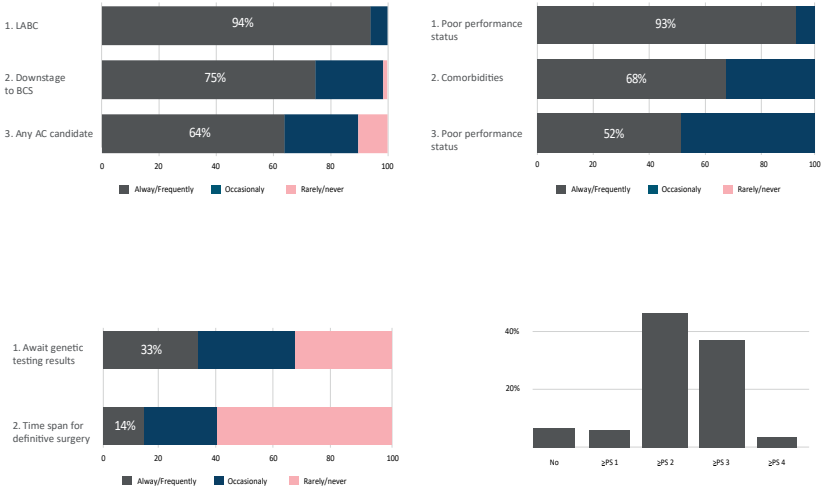

Figure 1A. Reported indications (tumour characteristics) for recommending NAC.
Figure 1B. Reported indications (clinical management factors) for recommending NAC.
Figure 1C. Reported contraindications (patient characteristics) for recommending NAC.
Figure 1D. Most common reported contraindication: performance status ≥ 2

DISCUSSION

This survey depicts the opinion of 138 Dutch surgical and medical oncologists from 64 out of 92 hospitals in the Netherlands on NAC in BC. Despite an international trend of increasing implementation for NAC in patients with early BC and the relatively high standard of care in the Netherlands, considerable variation in the use of NAC still exists between hospitals.

Respondents rated LABC as the most distinguished indication for NAC, in accordance with Dutch and international breast cancer guidelines[12]. In addition, the St. Gallen Breast Cancer Conference, that focuses exclusively on the primary therapy of early breast cancer, recommends to consider NAC based on tumour biology[14,15]. Our survey demonstrates that only 64% of clinicians recommends NAC instead of adjuvant chemotherapy when systemic therapy is indicated based on tumour biology. The actual NAC use is even lower based on NBCA-data (40% in BC stage II). With the increased evidence that subgroups of patients that achieve pCR after NAC do have a better prognosis in terms of disease-free and overall survival, NAC should nowadays be considered as a preferred option in the treatment of high risk triple negative BC and HER2 BC[3,4,16].

Another commonly accepted indication for NAC - confirmed by our survey - is to increase the chance of breast conservation surgery (BCS) without compromising the local recurrence rate. The ESMO guidelines on primary breast cancer advice primary systemic therapy in locally advanced and large operable cancers to allow for achieving operability or decreasing the extent of surgery[17]. In our survey, 75% of respondents recommend NAC to enable BCS. Contradictory, a relatively high percentage of 21% of respondents argued that BCS after NAC increases the risk of non-radical (i.e. resection with positive margins) resections. The restraint to use NAC to enable BCS may arise from the challenge for surgeons to determine the extent and original location of the residual lesion after NAC. More recently than our survey, a nationwide Dutch pathology study showed tumor-involved margins in 24.3% patients after BCS after NAC, compared to 103% after primary BSC[18]. According to Dutch National guidelines, a tumor-free margin is defined as the absence of tumor cells at the inked margins. Although surgical experiences have been improved by the introduction of iodine-125

seeds and ultrasound guided surgery, monitoring and localization techniques are still under research[19]. It is likely that clinicians' decisions towards NAC are mainly driven by surgical management goals, rather than tumour biology and survival.

Other incentives to consider NAC, such as time necessary for testing on hereditary breast cancer, are less frequently denominated as indication of importance. Only 33% of the clinicians recommends NAC to await genetic testing results, while the discovery of a BRCA1/2 mutation may influence treatment strategies. Also, extra time for patient work-up to plan the final type of reconstructive surgery is less frequently considered important. However, NAC has the potential for improving cosmetic outcomes in onco-plastic surgery[20]. Another important consideration described by clinicians in favour of chemotherapy prior to breast surgery is the possibility to asses anti-tumour activity and clinical efficacy of new treatments in neoadjuvant chemotherapy trials[21].

The survey also revealed concerns that prevented clinicians from recommending NAC. A patients' WHO-performance status of ≥2 was stated most frequently as reason to refrain from NAC, rather than advanced age. This is consistent with the idea that older patients, when selected correctly, can be treated safely with chemotherapy and that age only is no reason to refrain[22]. Although it can be questioned if these 138 experts represent the major opinion of NAC for breast cancer in the Netherlands, the main strength of this survey is that the respondents reflect practice preferences of 64 out of 89 Dutch hospitals: which means a 72% nationwide coverage, which stands for the treatment of almost 15.000 patients annually[10]. If this survey would be repeated, we expect same differences in opinions between experts' to be demonstrated. However, surveys rely heavily on the respondents' memory and opinion, thus bias should always be kept in mind when interpreting survey results.

CONCLUSION

Considerable variation exists in expert opinions on NAC for early breast cancer. This article highlights the complexity of decision making for early breast cancer patients and it emphasizes the need for more consensus among specialists on the indications for NAC in early BC patients.

Practice implications

The results of this survey highlight the importance of dynamic updates of reliable clinical practice guidelines, to standardize and ensure medical quality and safety. In other words: not only clinicians' awareness on multiple arguments in favour of the use of NAC could be improved, but also the sharing of considerations and experiences - as this brief report detailing clinical practices of Dutch surgical and medical oncologists - will speed up and clarify the implementation of NAC in early breast cancer. Ultimately, it is important that patients receive unambiguous and evidence-based treatment information in order to take part in a useful process of shared decision-making. The authors do not necessarily advocate that every patient should receive NAC; however, every patient eligible to NAC should receive a choice in chemotherapy timing. Another work by our group describes how patients perceived the choice in chemotherapy timing[23].

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SUPPLEMENT 1

20-question survey on the influence of patient, disease, and management related factors on decisions towards NAC.

General Information

1. What institute do you work for?
2. Are you working in an affiliated or other institute as well?
3. Sex m/v
4. Age
5. Specialism: surgeon / medical oncologist / other
6. Number of years in practice in current specialism (training excluded)
7. Number of new patients diagnosed with breast cancer treated per year

Diagnostics

8. Are the following diagnostic modalities typically applied prior to the commence of neoadjuvant chemotherapy (NAC)?

   MRI Never – Rarely – Sometimes – Often – Always

   PET-CT Never – Rarely – Sometimes – Often – Always

   Add comments

PART I. Indications and contraindications of NAC

9. Which items do you consider to be indications for the use of neoadjuvant chemotherapy (NAC)?

"Locally advanced disease (stage III)"

Never – Rarely – Sometimes – Often – Always

"Downstage to breast conserving surgery"

Never – Rarely – Sometimes – Often – Always

"Any adjuvant chemotherapy candidate / systemic therapy is indicated preoperatively"

Never – Rarely – Sometimes – Often – Always

"Await genetic testing results"

Never – Rarely – Sometimes – Often – Always

"Time span for definitive surgery"

Never – Rarely – Sometimes – Often – Always

Other/ add comments

10. Other / missing indications?

11. Ranking from 1 – 6 (most – less important) indication for neoadjuvant chemotherapy (NAC):

- ☐ Locally advanced disease (stage III)
- ☐ Downstage to breast conserving surgery
- ☐ Any adjuvant chemotherapy candidate /
- ☐ systemic therapy is indicated preoperatively
- ☐ Awaiting genetic testing results
- ☐ Time span for definitive surgery

12. Do you consider age to be a contraindication for the use of neoadjuvant chemotherapy (NAC)?

- ☐ No, age alone is no contraindication
- ☐ Yes, for patients aged <55
- ☐ Yes, for patients aged <60
- ☐ Yes, for patients aged <65
- ☐ Yes, for patients aged <70
- ☐ Yes, for patients aged <75

13. Do you consider the presence of comorbidities to be a contraindication for the use of neoadjuvant chemotherapy (NAC)?

According to the Charlson Index Scale:

- ☐ No, comorbidities are no contraindication
- ☐ Yes, for cardiac disease
- ☐ Yes, for vascular disease
- ☐ Yes, for pulmonary disease
- ☐ Yes, for neurological disease
- ☐ Yes, for gastrointestinal disease
- ☐ Yes, for urogenital disease
- ☐ Yes, for thrombotic disease
- ☐ Yes, for muscle and joint disease
- ☐ Yes, for endocrine system disease

Other/ add comments

14. Do you consider a poor performance status (PS) to be a contraindication for the use of neoadjuvant chemotherapy (NAC)?

According to the ECOG/WHO Performance Scale:

- ☐ No, a poor performance status is no contraindication
- ☐ Yes, if PS=0 – Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
- ☐ Yes, if PS=1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
- ☐ Yes, if PS=2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
- ☐ Yes, if PS=3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
- ☐ Yes, if PS=4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

15. Ranking from 1 – 3 (most – less important) contraindication:

- ☐ High age
- ☐ Comorbidities
- ☐ Poor performance status

15. Other / missing contraindications?

Part II. Other considerations that could influence the use of NAC

16. To what extent do you agree or disagree with the following statements?

"NAC improves the chance of achieving axillary conservation surgery"

Agree/Disagree

"NAC increases the risk of surgical complications"

Agree/Disagree

"Breast conservation surgery after NAC increases the risk of a non-radical resection"

Agree/Disagree

"Breast conservation surgery after NAC increases the risk of recurrence"

Agree/Disagree

"There is no evidence for an overall and disease-free survival benefit of NAC compared to AC"

Agree/Disagree

Add comments

Final section about study participation and interests

18. Number of new patients included in trials a year (national and international level)

>10 or <10

Other/ add comments

19. Do you visit one of the following conferences on a regular base?

- ☐ SABCS
- ☐ Bossche mammadagen (Dutch conference - annual conference for breast surgeons and medical oncologists)
- ☐ EBCC
- ☐ St. Gallen
- ☐ Chirurgendagen (Dutch conference – annual conference for surgeons in general)
- ☐ No, I never visit one of these conferences

Other/ add comments

20. Possibility to add any questions or comments

CHAPTER 4

Patients' experiences with decisions on timing of chemotherapy for breast cancer

P.E.R. Spronk[§]
K.M. de Ligt[§]
A.C.M. van Bommel
M.T.F.D. Vrancken Peeters
S. Siesling
C.H. Smorenburg
on behalf of the Nabon Breast Cancer Audit group
[§] both authors equally contributed to this article

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ABSTRACT

Introduction: Despite potential advantages, application of chemotherapy in the neo-adjuvant (NAC) instead of adjuvant (AC) setting for breast cancer (BC) patients varies among hospitals. The aim of this study was to gain insight in patients' experiences with decisions on the timing of chemotherapy for stage II and III BC.

Materials and methods: A 35-item online questionnaire was distributed among female patients (age>18) treated with either NAC or AC for clinical stage II/III invasive BC in 2013e2014 in the Netherlands. Outcome measures were the experienced exchange of information on the possible choice between both options and patients' involvement in the final decision on chemotherapy timing. Chemotherapy treatment experience was measured with the Cancer Therapy Satisfaction Questionnaire (CTSQ).

Results: Of 805 invited patients, 49% responded (179 NAC, 215 AC). NAC-treated patients were younger and more often treated in teaching/academic hospitals and high-volume hospitals. Information on the possibility of NAC was given to a minority of AC-treated patients (AC, stage II: 14%, stage III: 31%). Information on pros and cons of both NAC and AC was rated sufficient in about three fourth of respondents. Respondents not always felt having a choice in the timing of chemotherapy (stage II: 54% NAC vs 36% AC; stage III: 26% NAC, 54% AC).

Conclusion: The need to make a treatment decision on NAC was found to be made explicit in only a small number of adjuvant treated patients, in particular in BC stage II. Less than half of the respondents felt they had a real choice.

INTRODUCTION

Breast cancer (BC) care consists of a multidisciplinary approach of surgery, radiation, and systemic therapy including chemotherapy[1]. Chemotherapy intents to eliminate potential existing micrometastases, thus decreasing recurrence rates and mortality [2]; it is timed either prior to or following surgery, respectively neoadjuvant (NAC) or adjuvant (AC), both leading to similar disease free and overall survival[1,3,4]. NAC versus AC yields several advantages. Down-staging of the primary tumour increases resectability and the possibility of breast conserving surgery (BCS)[4] and axillary preserving surgery[5]. Moreover, the response to chemotherapy can be assessed[1,3,4,6], creating a platform to study the activity of (novel) agents or therapeutic combinations in a patient-personalized way [3,4,7,8].

(Inter)national BC guidelines recommend NAC over AC for patients with locally advanced BC (stage III) aged <70 years, while NAC can also be considered for patients with stage II BC with a clear indication for adjuvant chemotherapy[1,9,10]. The use of NAC for early BC is increasing, but despite its advantages, NAC is still applied less frequently than AC[11]. In the Netherlands, 12% of all newly diagnosed BC patients was treated with NAC in 2014, whereas in that same year 31% of patients received AC. Also, a considerable variation (0-97%) in NAC-application between hospitals was observed[12]. Significant predictors for the use of NAC (stage III) appeared to be young age, a diagnostic MRI, large tumour size, advanced nodal disease and a negative hormone receptor status.

However, not all variation could be explained by tumour and patient characteristics[13], implicating that other factors play a part in the timing of chemotherapy. Nowadays, treatment decisions are shared between the physician and patient. Important in the process of shared decision-making (SDM) is that both patient and physician are aware of a decision being required, knowing and understanding all available information on treatment options, and sharing the decision by incorporating both the physicians' advice as the patients' preferences[14]. Therefore, the goal of this study was to gain insight in patients' experiences with decisions on the timing of chemotherapy for stage II and III BC.

METHODS

Study population

Fifty-two hospitals were invited to participate; nineteen were willing to cooperate. We attempted an equal distribution in hospital volume (low, middle, high) and type (general, teaching, academic), and an equal geographical scatter. Patients of these hospitals were selected from the Netherlands Cancer Registry (NCR): a nationwide registry in which all newly diagnosed cancer patients are registered, hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), which includes all items for the NABON Breast Cancer Audit[12].

We selected surgically treated patients (aged 18 or older) who were diagnosed with primary invasive BC stage II/III between 2013 and 2014 and received NAC or AC. Patients with previous malignancies and/or metastases were excluded. A sub-set of 40-50 patients per participating hospital was randomly selected, with an average of 43 per hospital.

A total of 805 patients (367 NAC-treated, 438 AC-treated) were invited by a letter through their treating physician between August 24th, 2015 and January 1st, 2016 to participate in our online questionnaire. The survey was offered within a secured web-based environment named PROFILES[15]; paper questionnaires were provided on request. Completed questionnaires were collected until the 28st of February 2016. Respondents gave consent on an adjective (online) form for processing their answers and merging them to their clinical data available in the NCR. Approval from the Committee of Privacy of the NCR and the Medical Ethical Committee of the Netherlands Cancer Institute - Antoni van Leeuwenhoek were obtained for this study.

Questionnaire

The thirty-five-item questionnaire (**appendix A**) consisted of questions on SDM, completed with questions on the patients' experience and satisfaction with chemotherapy care in general. SDM was defined as by the study of Legare et al.: both health care provider and patient recognise and acknowledge that a decision is required, while knowing and understanding all best available relevant evidence, taking into account both the patient's preferences and the provider's advice [14].

Questions (Q) 1 to 9 asked about general mental and physical health and timing and type of chemotherapy received. The following questions dealt with the conditions of SDM. To determine whether patients were informed on the possible choice between NAC and AC, patients were asked whether they received information on chemotherapy prior to surgery (Q10) and whether (Q11) and with whom (oncologist, surgeon, nurse practitioner, nurse specialised on BC, general practitioner; Q12) NAC was discussed. To assess whether information on evidence of both options was provided, patients were asked if pros and cons of both NAC and AC were discussed (Q13). To determine if patient preferences were taken into account, questions were posed on whether the patient understood on what arguments the final decision was made (Q14 to Q17, Q19). The patients experienced SDM was based on questions whether they felt they shared the decision on the timing of chemotherapy (Q18) and had enough time to make a decision (Q20). In addition, to determine the overall level of patient information we asked questions on chemotherapy treatment information in general (Q21 to Q24). To determine chemotherapy treatment experience, all questions from the Cancer Therapy Satisfaction Questionnaire (CTSQ) were included (Q25 to Q30), consisting of three domains: Expectation of Therapy (EOT), Feelings about Side Effects (FSE), and Satisfaction With Therapy (SWT)[16]. General items such as nationality, level of education, and living and working status were requested as well (Q31 to Q35). A patient panel contacted through the Dutch BC patient association (Borstkankervereniging Nederland) critically reviewed and adjusted the questionnaire in comprehensible language and added additional explanations.

Analysis

Completed questionnaires were merged with the clinical data registered in the NCR. Generalisability of the results was determined by comparing characteristics of respondents to non-respondents (Pearson's chi-square). Furthermore, NAC-treated and AC-treated respondents were compared on patient, tumour, and treatment characteristics (Pearson's chi-square). The answers to the questionnaire were assessed separately for stage II and III; NAC-treated compared to AC-treated patients. Conditions of SDM were chi-square tested, as well as the experience with general information on chemotherapy (Q21 to Q24). At last, treatment experience was described by calculating CTSQ-scores[17]: a score between 0 and 100 was assessed separately for each domain for respondents that answered a minimum amount of questions. Higher scores are associated with better responses (better therapy expectations, feeling less impact of

side effects, and greater satisfaction with therapy). Means were calculated by the sum of all assessed scores divided by the number of respondents that a score was assessed to. Mean scores were compared using a T-test; we reported 95%-confidence intervals as well. Statistical significance was defined as a p-value <0.05 (two-sided). All analyses were performed in STATA 14.

RESULTS

Respondents to questionnaire (Table 1)

A response rate of 49% (394/805) was reached; 179 (45%) NAC-treated patients versus 215 (55%) AC-treated patients. Respondents did not differ significantly from the non-respondents on patient (age), tumour (year of diagnosis, clinical stage, morphology), and hospital characteristics (volume, type). The ratio of NAC versus AC was comparable between respondents and non-respondents.

NAC-treated respondents were more often treated in a teaching or academic hospital (including BC specialised hospitals) and in a high-volume hospital. Moreover, they were generally younger and had a higher SES, and were more often classified with clinical stage III disease (30%) compared to AC treated patients (7%). Also, there were more triple-negative and Her2-receptor positive tumours in the NAC-treated group. The majority of NAC-treated patients received breast conserving surgery for BC stage II (58%); AC-treated patients received a mastectomy more often (54%, all p<0.05).

Conditions of SDM (Table 2)

For BC stage II, 98% and 84% of NAC-treated and AC-treated patients, respectively, received information on chemotherapy prior to surgery (p=0.000). Among AC-treated patients, receiving information was more common in younger patients (p=0.061). Further on, information was provided four times as often by the medical oncologist for NAC-treated compared to AC-treated patients respectively (**Fig. 1**). If information on chemotherapy was provided prior to surgery, 100% of NAC-treated patients versus 14% of AC-treated patients received information on NAC as a possible treatment option (p=0.000); again, receiving information in the AC-group was more common in younger patients (p=0.009).

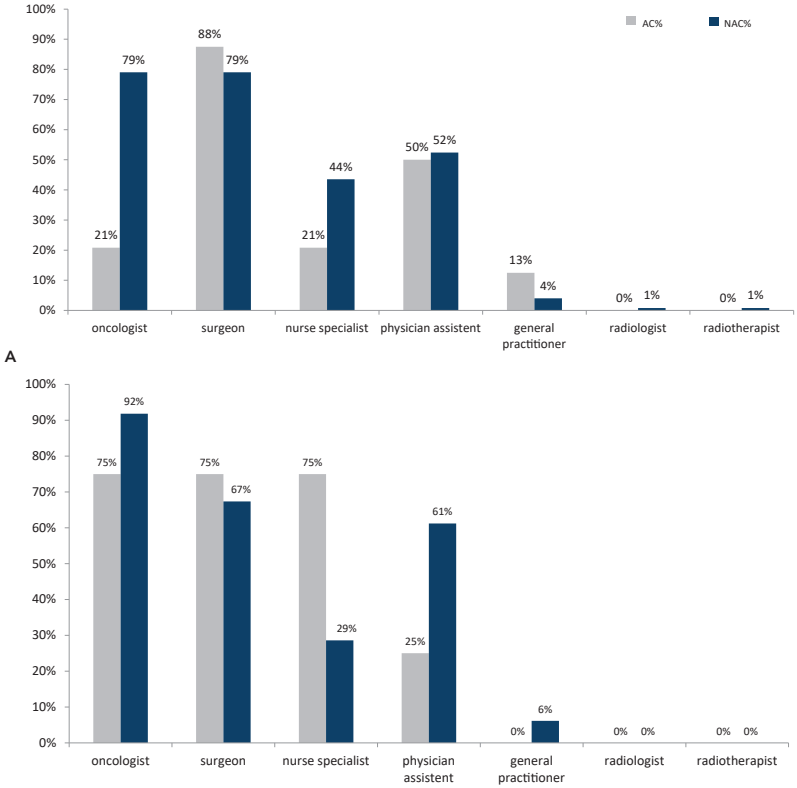

Figure 1. Information on chemotherapy provided prior to surgery by physicians during pre-surgical consultation(s), NAC vs AC, stage II (a) and stage III (b) separately (Q12).

Of all respondents that received information on NAC, 85% and 63% of NAC and AC-patients, respectively, stated they received sufficient evidence on the pros and cons of both NAC and AC (p = 0.008). Eventually, NAC-patients could explain more often why she and/or her physician decided the given treatment plan (97% NAC vs 66% AC, p=0.000).

For BC stage III, 92% and 93% of NAC and AC-treated patients, respectively, received prior to surgery any information on chemotherapy (p=0.959). Provided information on pros and cons of NAC was stated sufficient in both groups (p=0.947); almost every patient was able to explain why she and or her physician decided on either NAC or AC (p = 0.362) (**Table 2**).

Table 1. characteristics respondents treated with NAC vs AC

	NAC (n= 179)	(%)	AC (n=215)	(%)	P (Chi2)
Patient characteristics					
Age at diagnosis					
<40	19	11%	14	7%	
40-49	74	41%	65	30%	0.000
50-59	55	31%	58	27%	
60+	31	17%	78	36%	
Comorbidities					
None	119	66%	140	65%	
1	48	27%	59	27%	0.987
2 or more	10	6%	13	6%	
Missing	2	1%	3	1%	
Socio-economic status (SES)*					
High	65	36%	55	26%	0.008
Medium	73	41%	82	38%	
Low	41	23%	78	36%	
Education					
Secondary school (low level) or lower	19	11%	43	20%	
Secondary school (medium level)	38	21%	49	23%	
Secondary school (high level)	22	12%	26	12%	0.093
Intermediate vocational training (MBO)	39	22%	41	19%	
Higher vocational training (HBO) and university	58	32%	50	23%	
Other/unknown	3	2%	6	3%	
Tumour characteristics					
Stage (short), clinical					
II	126	70%	201	93%	0.000
III	53	30%	14	7%	
Hormone receptorstatus (based on biopsy supplemented with post-OK information)					
Triple negative	33	18%	29	13%	
Hormone-negative, Her2-positive	15	8%	14	7%	0.028
Hormone-positive, Her2-positive	29	16%	23	11%	
Hormone-positive, Her2-negative	99	55%	149	69%	
Unknown	3	2%	0	0%	
Treatment characteristics					
Type of surgery (based on final surgery)					
Stage II (clinical)					
Breast Conserving/Lumpectomy	73	58%	92	46%	0.032
Mastectomy	53	42%	109	54%	

Table 1. (continued)

	NAC (n= 179)	(%)	AC (n=215)	(%)	P (Chi2)
Stage III (clinical)					
Breast Conserving/Lumpectomy	14	26%	1	7%	0.124
Mastectomy	39	74%	13	93%	
Hospital characteristics					
Hospital type					
General	47	26%	79	37%	0.026
Teaching or academic (incl. BC specialised hospital)	132	74%	136	63%	
Hospital surgical volume **					
Low	58	32%	112	52%	0.000
Middle	77	43%	75	35%	
High	44	25%	28	13%	

* Socio-economic status (SES) of the patients was based on four-digit postal code at time of surgery; SES scores are provided by the Netherlands Institute for Social Research (Sociaal Cultureel Planbureau) and divided into three groups based on the delivered rank numbers: low (1st-3rd deciles), intermediate (4th-7th) and high (8th-10th) SES.
** Hospitals were categorised by surgical volume for primary breast cancer, defined as the mean annual number of BC surgeries during the period 2011-2015; categorised as low (<150), medium (150-300), and high (300<) volume.

The patient's opinion on SDM (Table 3, Fig. 2)

About half of all respondents with stage II BC (54% NAC, 36% AC) felt they had a real choice in their treatment plan (p=0.004); 68% and 50% of NAC-treated and AC-treated patients, respectively, described they wanted to decide themselves or shared their decision with their physician (**Fig. 2**). However, patients who stated they received information on the possibility of chemotherapy (Q10) and NAC specifically (Q11) in both groups felt equally involved in making a decision (54% NAC, 58% AC, p=0.854 (not in table)). For BC stage III, the treatment plan was already decided in 64% of NAC-treated patients and 50% of AC-treated patients (p=0.521) (**Table 3**).

Experience with general information on chemotherapy

No significant differences were found in the patients' experience with general information on chemotherapy. Over 95% of all respondents received information on their chemotherapy scheme and understood this information (95% NAC, 96% AC). Over 80% of respondents was informed on side-effects of their chemotherapy (NAC 88%, AC 84%). Both groups scored very high regarding understanding the information they received on chemotherapy (94% NAC, 96% AC). Respondents felt they had the opportunity to ask questions about chemotherapy (92% NAC, 95% AC).

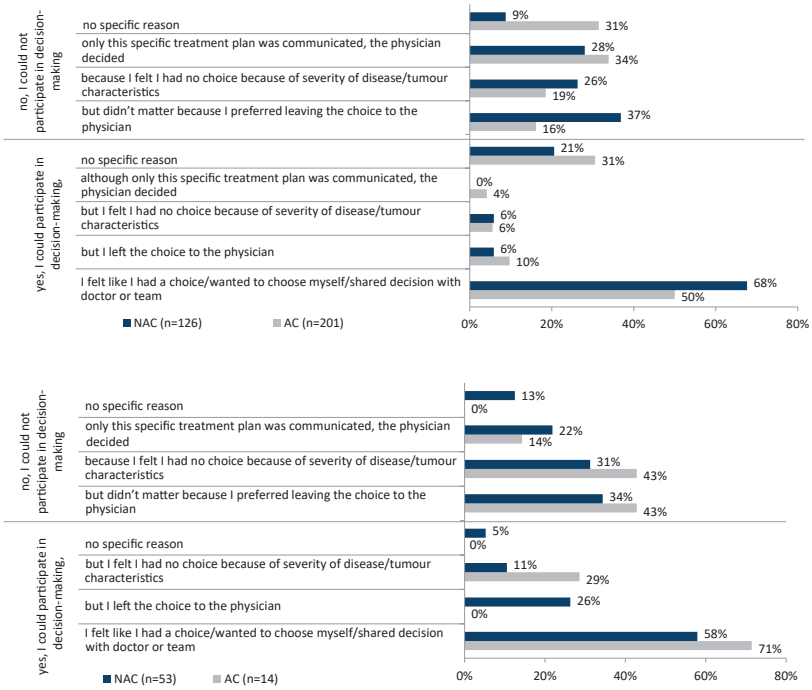

Figure 2. The patients opinion on SDM, separate for stage II (a) and III (b) (Q18, categorization of free text fields).

Treatment experience with chemotherapy (CTSQ, Fig. 3)

Significant differences between NAC-treated and AC-treated patients, respectively, were found in the treatment experience (**Fig. 3**). Mean EOT-scores for both NAC-treated and AC-treated patients were high (68 NAC, 68 AC; p=0.948), meaning that overall, respondents had a high believe in chemotherapy contributing to their cancer treatment. FSE-scores were moderate (46 NAC, 45 AC; p=0.714), meaning respondents felt their side effects were as severe as expected beforehand. In totality, NAC-treated patients were less satisfied with their chemotherapy than AC-treated patients (40 NAC, 42 AC; p=0.018).

Table 2. Conditions of Shared Decision-Making (SDM), NAC vs AC; separate for stage II and III

Q		NAC	(%)	AC	(%)	P (Chi2)
Stage II (n=126 NAC, 201 AC)						
10	Patients received information on chemotherapy in general before surgery (n=126 NAC, 201 AC)	124	98%	169	84%	0.000
11	Patient was given information about NAC (n=124 NAC, 169 AC)	124	100%	24	14%	0.000
13	Patient received sufficient information on pros and cons of both AC and NAC (n=124 NAC, 24 AC)	106	85%	15	63%	0.008
14, 16	Patient was able to explain why she and/or the physician chose for either NAC or AC (n= 126 NAC, 201 AC)	122	97%	132	66%	0.000
Stage III (n=53 NAC, 14 AC)						
10	Patients received information on chemotherapy in general before surgery (n=53 NAC, 14 AC)	49	92%	13	93%	0.959
11	Patient was given information about NAC (n=49 NAC, 13 AC)	49	100%	4	31%	0.000
13	Patient received sufficient information on pros and cons of both AC and NAC (n=49 NAC, 4 AC)	36	73%	3	75%	0.947
14, 16	Patient was able to explain why she and/or the physician chose for either NAC or AC (n=53 NAC, 14AC)	50	94%	14	100%	0.362

Table 3. The patients' opinion on Shared Decision-Making (SDM), NAC vs AC; separate for stage II and III

Q		NAC (n=126)	(%)	AC (n=201)	(%)	P (Chi2)
Stage II (n=126 AC, 201 AC)						
18	Patient felt she did have a choice in either choosing for NAC or AC (n=126 NAC, 201 AC)	68	54%	72	36%	0.008
20	Patient felt she had enough time to decide on either NAC or AC (n=68 NAC, 72 AC)	67	99%	72	100%	0.302
Stage III (n=53 NAC, 14 AC)						
18	Patient felt she did have a choice in either choosing for NAC or AC (n=53 NAC, 14AC)	19	36%	7	50%	0.521
20	Patient felt she had enough time to decide on either NAC or AC (n=19 NAC, 7 AC)	19	100%	7	100%	0.923

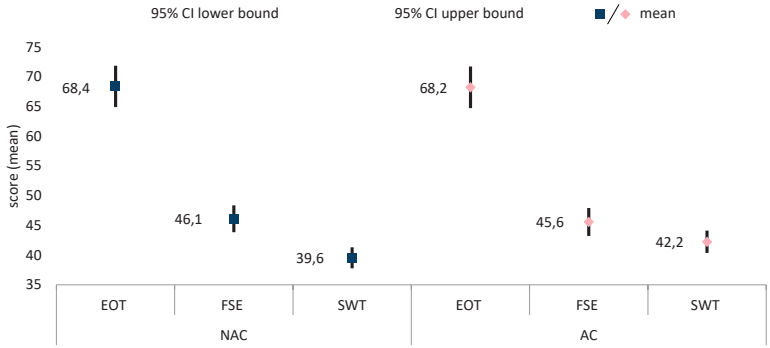

Figure 3. Treatment experience, mean CTSQ-scores per domain* and chemotherapy treatment, incl. 95% lower and upper confidence interval for NAC and AC separately (n ¼ 179 NAC,215 AC).*domains: Expectation of Therapy (EOT), Feelings about Side Effects (FSE), and Satisfaction With Therapy (SWT); range 0 (low score) to 100 (high score).

DISCUSSION

This study highlights important aspects in the decision-making process on the timing of chemotherapy (NAC vs AC) for early breast cancer. If information on chemotherapy was provided prior to surgery, 100% of NAC-treated patients versus 14% of AC-treated patients received information on NAC as a possible treatment option. Of those who received information on NAC, 85% and 63% of patients treated with NAC and AC, respectively, stated that they received sufficient evidence on the pros and cons of both NAC and AC.

The results of this survey confirm that the choice regarding either NAC or AC is often not discussed with patients with stage IIIII breast cancer prior to treatment. This suggests that clinicians rarely express that a treatment decision needs to be made, and patients may not realize that neoadjuvant treatment is a valid choice. In order to make a decision, sufficient information and relevant evidence on pros and cons of all treatment options should be provided before the start of therapy. Patients treated with AC were less informed about this treatment decision than NAC-treated respondents, and stage II respondents were less informed than stage III respondents.

Further on, both patients' and clinicians' preferences should be incorporated in treatment plans[14]. Few AC-treated respondents with BC stage II were able to explain reasons for adjuvant timing of systemic treatment instead of neoadjuvant timing. Moreover, about half of respondents did not feel they had a choice regarding timing of systemic treatment. These results reveal the impaired role of participation of patients in SDM on NAC.

Several potential explanations are present. First, the Dutch and international breast guidelines are straightforward about the recommendation of NAC for stage III BC[1,9,10], but the evidence of NAC for stage II BC is not included in the guidelines yet, since it is based on promising preliminary data and research[18,19]. Seemingly, treatment decisions are predominantly guideline-congruent, and when guidelines are not clear, clinicians' recommendations to patients are not uniform either. Consequently, differences in clinicians' opinions may lead to variation in treatment patterns, as confirmed by the NBCA audit results and other recent studies [11,13].

Moreover, clinicians' opinions exert one of the most powerful influences over patients' preferences[20]. Also, patients are often not aware that a treatment decision is required [20]. The health professional first speaking with the patient plays an important role in how information is conveyed, whether this is a surgeon, medical oncologist, nurse practitioner, or physician assistant. This will most likely drive the treatment decision. According to our survey, most of the information about NAC was provided by medical oncologists, of whom we expect stronger support for applying NAC than from surgeons. A referral from the surgeon to the medical oncologist defines whether a patient actually will have a consultation with an oncologist. In addition, appropriate information and additional support is essential to make quality decisions. Decision support-systems may help patients allow them to be primary decision maker[21]. Thirdly, the level of training of clinicians, conference attendance, and multidisciplinary meeting groups on a regular base may play a crucial role by creating more choice-awareness in preference-sensitive decisions.

Also, the preferred role of patients in preference-sensitive decisions is influenced by patients' age and education. Older and less educated patients are more likely to prefer a passive or collaborative role[22], whereas an active role is generally preferred by

younger and better educated patients[23]. We observed that NAC-treated patients treated were younger and better educated, while being better informed as well. Patient's participation in their treatment plan is important because a high level of involvement is associated with improved outcome in quality of life, physical and social functioning. Patient's involvement led to high levels of satisfaction with the decision and the subsequent treatment they received[24]. Even if the fit of treatment to preferences is not enhanced, the fact that patients are involved and felt meaningful to the situation may increase satisfaction[25]. Moreover, patients could be pleased to know whether their tumour responded or progressed on NAC, which can be valuable contribution under conditions of uncertainty.

Finally, the most common explanations for the application of NAC in stage II and stage III patients were tumour size and axillary metastases. These explanations correspond with reported results from cancer registries[11,13]. While NAC aims to downsize the tumour to improve the possibility of breast conservation surgery, it was expected that more respondents were treated with BCS after NAC[4,26]. However, in our survey the patient's desire for BCS was the major reason for NAC in only 28% of BC stage II patients. Valid options to refrain from chemotherapy (NAC or postoperative) may have been contraindications such as poor performance status or severe comorbidity. Also, it may be possible that women prefer to undergo surgery first, but these considerations should be clearly discussed.

Overall, the results of our study showed that general experience (CTSQ) with chemotherapy in terms of side effects was scored equal in both groups, but significant differences between groups were found in final satisfaction with care; NAC-treated patients seem to be less satisfied. The most likely explanation for this result, is the difference in approach in NAC-treated patients, in which NAC is commonly being used for down-staging of the tumour to increase resectability and enable BCS. When the response to chemotherapy appears to be disappointing and BCS does not seem possible, satisfaction could be less. Also, mostly young women receive NAC, which will have a big impact on their daily lives. However, these negative perceptions reiterate the importance of counselling support, communication, and expectation management.

Strengths and limitations

To our knowledge, this is the first study reflecting patients' experiences with decisions on the timing of chemotherapy for early BC. Previous literature focused mainly on experiences with decisions on adjuvant therapies for BC[27,28]. In the context of an increasing trend in NAC use[11,26], insight in patients' experience in SDM on NAC is extremely relevant.

Because of the connection between the clinical cancer registry and the patient reported experiences, this study is unique in design. We reached a high response rate of almost 400 respondents (49%) and selected a homogeneous comparable population compared to non-responders. The absolute number of BC stage III respondents was small, but because of the strict indication of NAC for these patients, this group was less relevant to discuss. Participation was opt-in, leading to selection bias in which those who responded were probably more critical on SDM then non-responders; providing paper questionnaires on request could lead to an underrepresentation of patients with lack of computer skills or access. Also, recall bias is a known limitation of all survey studies. Idem, creating a patient-comprehensible questionnaire is a difficult task. We were favoured by input from the Dutch patient association on breast cancer. Besides, we emphasize the fact that patient-reported data is based on the experience of patients, rather than a factual reflection of how decisions on chemotherapy timing were made. Furthermore, unfortunately, the numbers of respondents per hospital were too small to analyse intra-hospital variation in SDM; this would be interesting for further research.

CONCLUSION

In conclusion, our study revealed that the need to make a treatment decision on the timing of chemotherapy (NAC vs AC) for early breast cancer was discussed with only a small number of patients, in particular in BC stage II. Less than half of the respondents felt they had a real choice. Clinicians' opinions exert one of the most powerful influences over patients' preferences. National guidelines that are frequently updated and a continuous audit system integrating detection and real-time feedback will help in providing clear guidance to physicians for chemotherapy treatment timing with decision-making as a result of team work of all involved disciplines. By understanding patient preferences and incorporating them into treatment decisions, it will be possible to reduce unwarranted variations and deliver appropriate patient-centered care.

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APPENDIX A

35-question item questionnaire consisted of questions on SDM, patients' experiences on timing of chemotherapy and satisfaction with chemotherapy care in general.

0. What is your date of birth?
..-..-19..

1. How was, in your own perception, your physical health over the past three months?
Excellent – very well – well – moderate – bad

2. How was, in your own perception, your mental health over the past three months?
Excellent – very well – well – moderate – bad

3. At time of your treatment with chemotherapy, did you suffer from one or more of undermentioned diseases?
Any other type of cancer – lung disease - cardiovascular disease – gastro-intestinal disease – illness of urinary or reproductive system – musco-skeletal disease - central nerve system – illness of metabolism or coagulopathy - infectious disease – none – other

4. Were you menopausal at time of your treatment with chemotherapy?
Premenopausal – perimenopausal – postmenopausal – I don't know – not applicable

5. Were you treated with chemotherapy anterior or posterior to your surgical treatment for breast cancer?
Anterior (neoadjuvant chemotherapy) – posterior (adjuvant chemotherapy) – both anterior as posterior (combination of neoadjuvant and adjuvant)

6. Which type of chemotherapy did you receive at the start of your chemotherapy treatment?
TAC – AC – FEC – FEC followed by taxane – AC followed by taxane – Trastuzumab (Herceptin) and chemotherapy – I don't know – other

7. How many courses of chemotherapy treatment did you receive?
.. courses

8. **Did you finish the total amount of chemotherapy courses that were planned for you?**
Yes (proceed with question 10) – no (proceed with question 9)

9. **What was the reason for premature termination of your chemotherapy treatment?**
Because of (severe) side effects – by own preference – the chemotherapy did not (sufficient) affect the cancer – I don't know – other

10. **Was the necessity of chemotherapy within your treatment plan discussed with you previous to receiving your surgical treatment?**
Yes – no – I don't know

11. **Was the option of starting with chemotherapy prior to surgery discussed with you previous to receiving your surgical treatment?**
Yes – no – I don't know

12. **With whom did you discuss treatment with chemotherapy prior to surgery?**
Oncologist – surgeon – nurse practitioner – breast cancer nurse – general practitioner – other

13. **Did you receive information on the pros and cons of both treatment with chemotherapy initiated either prior or subsequently to surgical treatment?**
Yes – yes, but not as much as I preferred – no – I don't know

14. **Do you know why you were treated with chemotherapy prior to receiving surgery?**
Not applicable, I received adjuvant chemotherapy treatment – No, I don't know – Yes, I do know

15. **In case you do know why you were treated with chemotherapy prior to surgery, what was the reason for choosing this treatment option?**
Tumour size – axillary metastases – preferring a breast conserving surgery – to stretch time to surgery – my physician decided this – my physician decided this, because… - I don't know – other

16. **Do you know why you were treated with chemotherapy after receiving surgery?**
Not applicable, I received neoadjuvant chemotherapy treatment – No, I don't know – Yes, I do know

17. In case you do know why you were treated with chemotherapy after receiving surgery, what was the reason for choosing this treatment option?
Tumour size – axillary metastases – I preferred this type of chemotherapy – my physician decided this – my physician decided this, because… - I don't know – other

18. Do you feel you could co-decide with your physician on treatment with chemotherapy either prior or after receiving surgery?
Yes, because… - no, because…

19. Who helped you in deciding on chemotherapy treatment order?
I decided myself – my physician – my partner – family – friends – information on the internet - patient association – 'fellow-sufferers' – other

20. Do you feel you had enough time to decide on chemotherapy treatment order?
Yes – no

21. Was the chemotherapy treatment scheme explained clearly to you?
Yes, and I fully understood the explanation – yes, but I did not fully understand the explanation – no – I don't know

22. Were the side effects of chemotherapy explained prior to receiving chemotherapy?
Yes, prior to treatment and sufficient – Yes, prior to treatment but not sufficient – Yes, but not prior to treatment – No – I don't know

23. Did you understand the information you received on chemotherapy?
Yes – no – not applicable, I received no information on chemotherapy in general – I don't know

24. Was there the opportunity to ask questions to your physician on chemotherapy?
Yes, sufficient – yes, somewhat – no – I don't know

25. How often during chemotherapy treatment did you feel that..
(never – rarely – sometimes – mostly – always)

a. chemotherapy would help you to return to a normal life?
b. chemotherapy would get rid of the cancer?
c. chemotherapy would help prevent the cancer from coming back?
d. chemotherapy would stop the cancer from spreading?

e. chemotherapy limited your daily activities?
f. Upset about side effects?
g. chemotherapy was worth taking even with side effects?
h. chemotherapy would help you live longer?
i. How often did you think about stopping chemotherapy?

26. Overall, how worthwhile was your chemotherapy?
Very worthwhile – pretty worthwhile – fairly worthwhile – a little worthwhile – not worthwhile

27. Overall, was taking chemotherapy as difficult as expected?
A lot more difficult – slightly more difficult – as difficult as I expected – slightly easier – a lot easier

28.a. Overall, how well did the benefits of chemotherapy meet your expectations?

28.b. Overall, were side effects as expected?
A lot better/more than expected – slightly better/more than expected – met my expectations – slightly less than expected – a lot less than expected

29.a. How satisfied were you with the form of your chemotherapy?

29.b. How satisfied were you with your most recent chemotherapy?
Very satisfied – satisfied – neither satisfied nor dissatisfied – dissatisfied – very dissatisfied

30.a. If given choice again, would you decide to take this chemotherapy treatment?

30.b. Would you recommend this type of chemotherapy to others in a similar situation?
Absolutely – probably – I don't know – probably not – absolutely not

31. At time of your breast cancer treatment, what were the four digits of your postal code?
_ _ _ _

32. What is your highest completed education? (completed with diploma or certificate)
No education – lower education – middle education – higher education – other

33. What is currently your marital status?

Married/relationship – divorced/separated – widow/widower/partner diseased – single

34. What description is most applicable to you at this moment? (please tick one answer)

Attending school/education – paid employment – unemployed/seeking work – incapacitated – housewife – retirement

35. What is your nationality?

Dutch – Moroccan – Surinamese – Turkish – German – Belgian – Other

Do you have any questions/remarks?

CHAPTER 5

Breast conserving therapy after neoadjuvant chemotherapy; data from the Dutch Breast Cancer Audit

P.E.R. Spronk
J.H. Volders
P. van den Tol
C.H. Smorenburg
M.T.F.D. Vrancken Peeters

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ABSTRACT

Introduction: NAC has led to an increase in breast conserving surgery (BCS) worldwide. This study aims to analyse trends in the use of neoadjuvant chemotherapy (NAC) and the impact on surgical outcomes.

Methods: We reviewed all records of cT1-4N0-3M0 breast cancer patients diagnosed between July 2011 and June 2016 who have been registered in the Dutch National Breast Cancer Audit (NBCA) (N=57.177). The surgical outcomes of 'BCS after NAC' were compared with 'primary BCS', using a multivariable logistic regression model.

Results: Between 2011 and 2016, the use of NAC increased from 9% to 18% and 'BCS after NAC' (N = 4170) increased from 43% to 57%. We observed an involved invasive margin rate (IMR) of 6,7% and a re-excision rate of 6,6%. As compared to 'primary BCS', the IMR of 'BCS after NAC' is higher for cT1 (12,3% versus 8,3%; $p < 0.005$), equal for cT2 (14% versus 14%; $p=0.046$) and lower for cT3 breast cancer (28,3% versus 31%; $p<0.005$). Prognostic factors associated with IMR for both 'primary BCS' as for 'BCS after NAC' are: lobular invasive breast cancer and a hormone receptor positive receptor status (all $p<0,005$).

Conclusion: The use of NAC and the incidence of 'BCS after NAC' increased exponentially in time for all stages of invasive breast cancer in the Netherlands. This nationwide data confirms that 'BCS after NAC' compared to 'primary BCS' leads to equal surgical outcomes for cT2 and improved surgical outcomes for cT3 breast cancer. These promising results encourage current developments towards de-escalation of surgical treatment.

INTRODUCTION

Neoadjuvant chemotherapy in breast cancer patients has resulted in an increased rate of breast conserving treatment (BCT) consisting of breast conserving surgery (BCS) and radiation treatment[1-3]. Due to down-staging of the tumour by NAC, patients who were initially planned for mastectomy could receive BCS. The advantages of BCS compared to mastectomy obviously include less morbidity and thereby improved aspects of quality of life[3-5]. Another benefit of NAC includes the opportunity to deescalate surgical treatment of the axilla[6-8]. BCS after NAC introduces challenges as identification of original tumour location and monitoring tumour response using imaging[9,10]. The efficacy of NAC to downsize or achieve a pathologic complete response (pCR) has improved due to more efficient targeted drug regimens, and pCR rates of up to 60-80% in the triple negative and HR-/ HER2. subtypes are now being reached[11,12]. These promising results have led to challenging new trials investigating the potential of non-operative therapy for invasive breast cancer by utilizing accurate image-guided percutaneous biopsy to document pathologic complete response[13-15].

While improved breast imaging and the promising concept of non-operative therapy in patients that reach pCR after NAC are currently being investigated, surgical management with the primary goal to remove the (residual) tumour with clear margins is still the standard of care. In the present study, we analyse trends in the surgical performance after NAC for breast cancer in the Netherlands between 2012 and 2016 (1), we describe the surgical outcomes including margins and re-excision rates for BCS after NAC compared to primary BCS (2) and identify prognostic factors associated with involved margins for both groups (3).

METHODS

The NBCA

The NABON Breast Cancer Audit (NBCA) is a multidisciplinary nationwide registry of all diagnostic and treatment modalities of patients who are surgically treated for newly diagnosed breast cancer in the Netherlands. All 89 hospitals in the Netherlands participating in breast cancer care participate in this nationwide registry. Data completeness of the NBCA is estimated to be at least 95%. Available data from the NBCA dataset include demographic variables (year of incidence, age), tumour variables (histologic subtype, clinical tumour stage, clinical nodal stage and hormone receptor status) and treatment variables (use of systemic therapy, radiotherapy and type of surgery). Furthermore, the volume and type of hospital is being registered. Hospital volume was based on the surgical volume, which was defined as the mean annual number of breast cancer surgeries during the period 2012-2016. The cut-off points of <150 and 300<, were based on those reported in a publication of the European Society of Breast Cancer Specialist (EUSOMA)[16]. Hospital type was described as academic, teaching and general. Academic hospitals are part of a university, and both academic and teaching hospitals provide medical training to surgical residents.

Data selection

Data records of patients aged 18-98 years diagnosed with cT1-4N0-3M0 invasive breast cancer between July 2011 and June 2016 were abstracted from the NBCA. We excluded patients with a prior cancer diagnosis or unknown timing of chemotherapy. Neoadjuvant chemotherapy (NAC)was defined as chemotherapy given within four weeks prior to surgery. In accordance with international guidelines, the Dutch national breast cancer guidelines indicate NAC for patients with locally advanced disease (stage III) and recommended it in patients with stage II disease with an indication for systemic treatment[17,18]. Trends in the use of NAC and the surgical performance after NAC during the years were analysed.

Surgical performance

Type of surgery (BCS or mastectomy) and the pathology report of the surgical specimen was derived from the NBCA database. Resection margins of the surgical specimen were defined according to the Dutch guidelines and in accordance with the definition

of the quality indicator defined by the NBCA audit[19]. In the Dutch guidelines, the definition for focally involved margins for invasive breast cancer is described as residual tumour in the resection surface over a maximum length of 4 mm. More than focally involved margins is defined as residual tumour in the resection surface over more than 4 mm. According to the Dutch guidelines, focally involved margins do not mandate re-excision. In case of more than focally involved (positive) margins, a re-excision is indicated unless the positive margin is the dorsal margin and the fascia has been resected. In addition to radiation after BCS, a radiation therapy boost may be applied when one or more of the following indications is present: age <50 years, an estimated local recurrences risk 1% per year, grade 3, positive tumour margins and lymphvascular space invasion[20,21].

Statistical analysis

Statistical analysis was performed in PASW Statistics version 20 (SPSS inc Chicago, IL, USA). Descriptive analyses were used to report on the trends in the use of NAC and in the surgical outcomes after NAC. Bivariate comparisons of surgical outcomes of BCS with and without NAC were performed with chi-square tests. Secondly, a multivariable logistic regression model was used to determine which factors were independent associated for tumour involved margins in BCS with and without NAC. Statistical tests were 2-sided and statistical significance was defined as a p value <0.05.

RESULTS

Overall, 62.982 patients were diagnosed with cT1-4N0-3M0 invasive breast cancer in the Netherlands between July 2011 and June 2016, and registered in the NBCA registry. Patients with a prior cancer diagnosis (N=5661) or unknown timing of chemotherapy (N=144) were excluded for further analyses, resulting in data of 57.177 patients available for our study. Median age was 62 years (range 19-98) and most of the patients were diagnosed with a clinical tumour stage of cT1 (N=34.678; 60,7%) or cT2 (N=18.482; 32,3%), without nodal involvement (N=47.512; 83,1%).

Primary surgery without NAC was performed in 85.8% of all patients (N=49.712); of which 65% were treated with BCS (N=32.305) and 35% with a mastectomy (N=17.407).

Table 1. Clinical-pathological and hospital characteristics of patients with invasive cT1-4M0 breast cancer (N=8195) who have received NAC followed by surgery (2012-2016).

	NAC + BCS		NAC + Mastectomy		
	(N=4170)		(N=4025)		
Year of incidence					*<0,005*
2012 (07-2011 – 06-2012)	424	*43%*	553	57%	
2013 (07-2012 – 06-2013)	626	*47%*	716	53%	
2014 (07-2013 – 06-2014)	836	*50%*	838	50%	
2015 (07-2014 – 06-2015)	1086	*52%*	1008	48%	
2016 (07-2015 – 06-2016)	1198	*57%*	910	43%	
Age					*<0,005*
<40	395	*39%*	626	*61%*	
40-50	1307	*49%*	1341	*51%*	
50-60	1462	*55%*	1173	*45%*	
60-70	872	*55%*	704	*45%*	
70-100	132	*42%*	181	*58%*	
Histologic subtype					*<0,005*
Ductal	3633	*53%*	3287	48%	
Lobular	331	*41%*	482	59%	
DCIS component					*0,009*
No	2684	*52%*	2463	*48%*	
Yes	1486	*49%*	1562	*51%*	
Clinical tumor stage					*<0,005*
cT1	706	*59%*	488	*41%*	
cT2	2948	*63%*	1763	*37%*	
cT3	442	*26%*	1246	*74%*	
cT4	74	*12%*	528	*88%*	
Clinical nodal stage					*<0,005*
cN0	1976	*59%*	1401	41%	
cN1	1921	*47%*	2164	53%	
cN2	80	*38%*	128	62%	
cN3	192	*37%*	329	63%	
Hormone receptor status					*0,007*
Triple -	890	*55%*	743	*45%*	
HR -, HER2+	338	*48%*	367	*52%*	
HR +, HER2+	610	*54%*	529	*46%*	
HR +, HER2-	2237	*50%*	2267	*50%*	
Type of hospital					*0,016*
General-	1356	*50%*	1331	*50%*	

Table 1. (continued)

	NAC + BCS		NAC + Mastectomy		
	(N=4170)		(N=4025)		
Teaching-	1987	*50%*	2004	*50%*	
Academic-	827	*55%*	690	*45%*	
Hospital surgical volume					*0,472*
< 150	1043	*51%*	988	*49%*	
150-300	1557	*50%*	1531	*50%*	
> 300	1562	*51%*	1493	*49%*	

In 14.2% of patients NAC was applied before surgery (N=8195); of which 50.9% were treated with BCS (N=4170) and 49.1% with a mastectomy (N=4025). Clinical-pathological and hospital characteristics of patients treated with NAC are shown in **Table 1**. Women who received NAC followed by BCS instead of a mastectomy tended to be older (>50 yrs of age), except of patients aged >70 years of age. Tumour characteristics associated with NAC followed by BCS are ductal invasive histologic subtype, no multifocality, a cT1-2 clinical tumour stage and cN0 disease (all P<0.005).

Between 2011 and 2016, there were 37 general-, 43 teaching and 9 academic hospitals in the Netherlands; divided into low-volume <150 (N=44), mid-range 150-300 (N=34) and high-volume 300< (N=11) hospitals. NAC was most often applied in academic hospitals (26% NAC; N=1517) compared to teaching- (13% NAC; N=3991) and general hospitals (12% NAC; N=2687). The type or volume of hospital is not associated with the type of surgery received after NAC [Table 1].

Trends in the surgical performance after NAC

In the last 5 years the use of NAC increased from 9% in 2012 to 18% in 2016 and applies to the clinical tumour stages cT1-3 [**Table 2**]. There is no increasing trend in the use of NAC for cT4 breast cancer (a stable percentage around 63% over the years). A greater upward trend per tumour stage in the use of NAC is seen in the sub selection of patients with nodal involvement (N=9665); the use of NAC increased from 38% (N=636) in 2012 to 61% (N=1168) in 2016; for cT1N+ from 17% (N=80) to 38% (N=169), for cT2N+ from 35% (N=289) to 63% (N= 613) and for cT3N+ from 67% (N=159) to 80% (N=283).

Table 2. Patients with invasive cT1-4M0 breast cancer who have received NAC followed by surgery, per tumour stage; 2012 compared to 2016.

	Total	NAC	%	Followed by surgery		No NAC	%	Primary surgery	
2012				BCS	Mastectomy			BCS	Mastectomy
cT1	6600	129	2%	52%	48%	6471	98%	74%	26%
cT2	3445	508	15%	60%	40%	2937	85%	44%	56%
cT3	475	216	45%	20%	80%	259	55%	5%	95%
cT4	197	124	63%	8%	92%	73	37%	8%	92%
cT1-4	10717	977	9%	43%	57%	9740	91%	63%	37%
2016									
cT1	7161	335	5%	65%	35%	6828	95%	79%	21%
cT2	3768	1271	33%	66%	34%	2526	67%	48%	52%
cT3	666	432	62%	35%	65%	256	38%	9%	91%
cT4	198	153	62%	19%	81%	75	38%	17%	83%
cT1-4	11793	153	18%	57%	43%	9685	82%	68%	32%

As presented in Table 1, 'BCS after NAC' increased from 43% in 2012 to 57% in 2016, which is a relative increase of 33%. For 'Primary BCS', an increased percentage of 63% in 2012 to 69% in 2016 is observed, which is a relative increase of only 9,5%. As depicted in **Fig. 1A**, an upward trend of 'BCS after NAC' for cT1N0 breast cancer is described from 43% (N=20) to 61% (N=99), for cT2N0 from 65% (N=139) to 70% (N=437) and for cT3N0 from 30% (N=14) to 43% (N=54). Shown in **Fig. 1B**, an equal upward trend of 'BCS after NAC' is seen in the sub selection of patients with nodal involvement; for cT1N+ from 58% (N=46) to 69% (N=116), for cT2N+ from 56% (N=161) to 62% (N=377) and for cT3N+ from 18% (N=29) to 31% (N=87). The group of cT4 breast cancer patients treated is too small for reliable analyses (N<110 of patients treated with NAC per year).

For 'Primary BCS', increased percentages of more BCS per tumour stage is observed. However, this increase is to a lesser extent; from 76% to 80% for cT1N0, from 49% to 51% for cT2N0 and from 6% to 11% for cT3N0. For patients with nodal involvement: from 51% to 58% for cT1N+, from 24% to 26% for cT2N+ and from 4% to 6% for cT3N+.

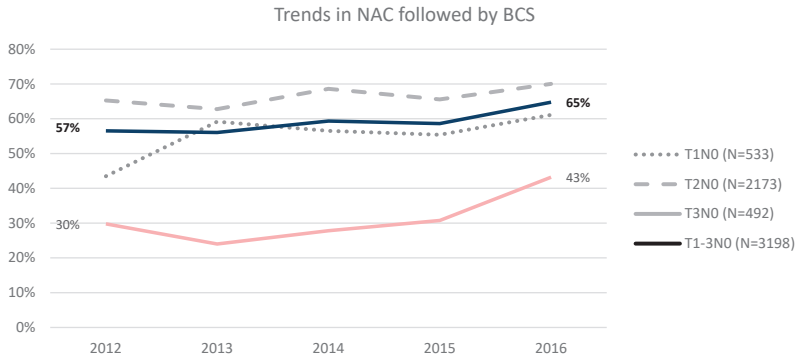

Figure 1a. Trends in NAC followed by BCS per tumour stage in patients with cN0 disease; 2012-2016.
*N= patients treated with NAC.

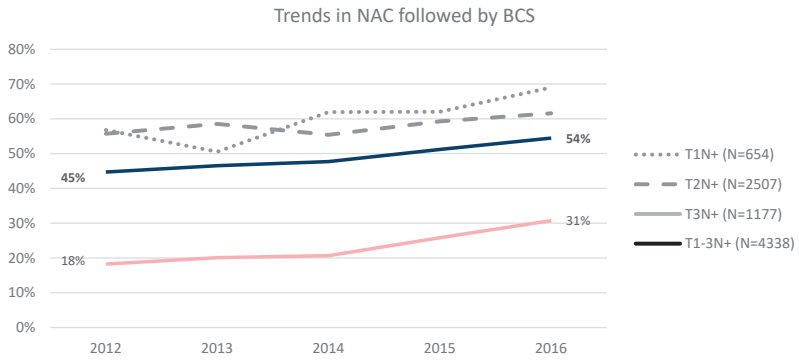

Figure 1b. Trends in NAC followed by BCS per tumour stage in patients with nodal involvement; 2012-2016.
*N= patients treated with NAC.

Surgical outcomes of BCS after NAC

Table 3 shows the surgical outcomes of 'BCS after NAC' in terms of focally or more than focally involved invasive margins and re-excision rates. Of all patients treated with BCS after NAC between 2011 and 2016 (N=4170), 8,5% (N=355) had focally involved invasive margins and 6,7% (N=281) had more than focally involved invasive margins. The re-excision rate was 6,6%; consisting of almost all patients with more than focally involved margins. For primary BCS (N=32.305), these percentages are 6,3% and 3,1% respectively, resulting in a 5,3% overall re-excision rate.

Table 3. Surgical outcomes of patients with invasive cT1-4M0 breast cancer who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).
* This is excl. patients with invasive cT1-4M0 breast cancer without DCIS involvement

	NAC + BCS (N=4170)		Primary BCS (N=32.305)		
Involved margins (Invasive or DCIS)					*<0,005*
> focally	286	6,9%	1075	3,3%	
Focally	439	10,5%	3124	9,7%	
No	3391	81,3%	27994	86,7%	
Involved invasive margins					*<0,005*
> focally invasive	281	6,7%	1001	3,1%	
Focally invasive	355	8,5%	2021	6,3%	
No	3480	83,5%	29171	90,3%	
Involved DCIS margins*					*0,107*
> focally DCIS	32	2,3%	510	3,3%	
Focally DCIS	126	9,1%	1423	9,3%	
No	1229	88,6%	13342	87,3%	
Re-excision					*<0,005*
No	3823	91,7%	29309	90,7%	
Yes	275	6,6%	1699	5,3%	
missing	72	1,7%	1297	4,0%	
Type of re-excision					*0,661*
BCS	146	53,1%	933	54,9%	
Mastectomy	129	46,9%	764	45,0%	

On multivariable analysis, prognostic factors associated with involved invasive margins for both patients treated with primary BCS as for BCS after NAC are: lobular invasive breast cancer, an increasing clinical tumour stage and a hormone receptor positive receptor status (all p<0,005; **Table 4**). The type of hospital, the year of incidence, a DCIS component and nodal involvement are only associated with involved invasive margins for primary BCS (all p<0,005). From a sub-analysis on re-excision rates, lobular invasive breast cancer was the only significant factor associated with a mastectomy if a re-excision was performed because of involved margins in BCS after NAC.

As shown in Fig. 2, there is a significant difference in involved invasive margins (in terms of focally or more than focally) in patients treated with BCS after NAC compared to patients treated with primary BCS per tumour stage. While the percentage of involved

Table 4. Multivariable logistic regression for the odds of involved invasive margins in patients with invasive cT1-4M0 breast cancer who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).

	NAC + BCS (N=4116)				Primary BCS (N=32.193)			
		95% CI				95% CI		
	OR	Lower	Upper		OR	Lower	Upper	
Year of incidence				*0,318*				*<0,005*
2012	ref.				ref.			
2013	1,158	0,784	1,712		0,823	0,721	0,939	
2014	0,881	0,602	1,291		0,79	0,694	0,9	
2015	1,186	0,828	1,698		0,831	0,73	0,947	
2016	1,113	0,78	1,587		0,793	0,696	0,904	
Age				*0,561*				*0,038*
<40	0,912	0,62	1,343		0,977	0,703	1,359	
40-50	1,02	0,805	1,292		1,126	0,973	1,302	
50-60	ref.				ref.			
60-70	1,107	0,856	1,431		0,919	0,825	1,023	
70-100	0,649	0,335	1,258		1,05	0,939	1,174	
Histologic subtype				*<0,005*				*<0,005*
Ductal	ref.				ref.			
Lobular	4,684	3,559	6,165		2,912	2,602	3,259	
DCIS component				*0,024*				*<0,005*
No	ref.				ref.			
Yes	1,273	1,032	1,57		1,182	1,081	1,292	
Clinical tumor stage				*<0,005*				*<0,005*
cT1	ref.				ref.			
cT2	1,275	0,966	1,683		1,676	1,523	1,844	
cT3	2,622	1,837	3,744		3,202	1,853	5,532	
cT4	3,333	1,805	6,157		2,904	1,365	6,178	
Clinical nodal stage				*0,017*				*<0,005*
cN0	ref.				ref.			
cN1	1,291	1,054	1,581		1,664	1,419	1,952	
cN2	2,013	1,06	3,822		2,639	1,187	5,867	
cN3	1,49	0,928	2,393		4,776	1,736	13,138	
Hormone receptor status				*<0,005*				*<0,005*
Triple -	1,311	0,627	2,742		0,523	0,433	0,633	
HR -, HER2+	ref.	0,064	0,233		ref.	0,064	0,233	
HR +, HER2+	2,908	1,444	5,86		0,709	0,523	0,962	
HR +, HER2-	8,184	4,29	15,612		0,844	0,714	0,998	
Type of hospital				*0,035*				*<0,005*
General-	1,118	0,88	1,421		1,148	1,044	1,263	

Table 4. (continued)

	NAC + BCS (N=4116)				Primary BCS (N=32.193)			
		95% CI				95% CI		
	OR	**Lower**	**Upper**		**OR**	**Lower**	**Upper**	
Teaching-	ref.				ref.			
Academic-	1,405	1,086	1,817		1,254	1,085	1,449	
Hospital surgical volume				*0,956*				*0,031*
< 150	ref.				ref.			
150-300	0,986	0,752	1,294		1,029	0,921	1,151	
> 300	1,021	0,787	1,325		0,907	0,812	1,012	

invasive margins (IMR) for cT1 patients treated with BCS after NAC is higher than after primary BCS (12,3% compared to 8,3%; p<0,005) and comparable for cT2 patients (14,0% compared to 13,7%; p=0,046), the percentage of IMR is significant lower for cT3 patients treated with BCS after NAC compared to primary BCS (28,3% versus 31,0%; p<0.005).

When we analysed the data for cT3 patients, lobular invasive breast cancer and a hormone receptor positive receptor status were associated with IMR, with no difference between patients receiving NAC and patients receiving no NAC.

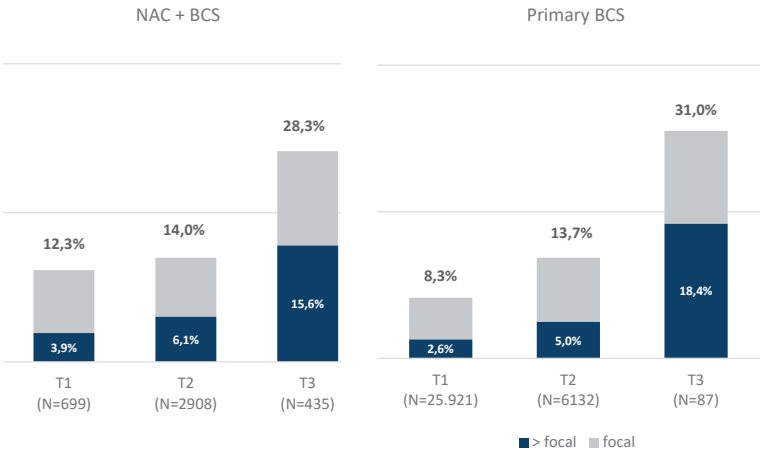

Figure 2. Percentage of patients with invasive cT1-4M0 breast cancer and involved invasive margins who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).

DISCUSSION

This population-based study showed an increase in the use of NAC from 9% in 2011 to 18% in 2016 and an increase of more 'BCS after NAC' from 43% to 57% compared to 'primary BCS' from 63% to 68% in patients with primary breast cancer in the Netherlands. The increasing implementation of NAC is consistent with previous studies on the trend of NAC in breast cancer care[22-24]. Together with this international trend, it is demonstrated that NAC increases the rates of breast preservation in tumours of >2 cm[25,26]. However, this study shows an increasing trend towards more BCS after NAC not only for larger tumours but for all stages of breast cancer.

There are several explanations for this upward trend towards more 'BCS after NAC' for all stages of disease. With the increased evidence that subgroups of patients who achieve a complete pathological tumour (pCR) after NAC do have a better prognosis in terms of disease-free and overall survival, NAC is nowadays be considered as a preferred option in the treatment of triple negative and HER2. breast cancer[27-29]. Secondly, the amount of a pCR response reported has increased dramatically in the past years because of improvements of targeted therapies. Up to half of the patients in specific groups such as her2-positive patients achieve a complete remission after NAC, which has subsequently led to more BCS[30-33]. Furthermore, the development of innovative approaches to axillary staging after chemotherapy has most likely contributed to more BCS followed by NAC in patients with nodal involvement at diagnosis[6,8,34,35]. Thereby, the growing experience and confidence with NAC among clinicians due to information from nationwide clinical quality registries, the use of quality indicators providing benchmark information on surgical outcomes and the exchange of knowledge by a multidisciplinary approach and cross-border hospital collaborations may all be attributed to the upward trend towards more BCS after NAC.

The involved invasive margin rate in our study is 6,7% for 'BCS after NAC' compared to 3,1% for 'primary BCS'. The overall positive margin rate in our study is 6,9% for 'BCS after NAC' compared to 3,3% for 'primary BCS'. These rates are relatively low compared to other studies. In a systematic review performed by Volders et al. in which they aimed to determine surgical outcomes for BCS after NAC, involved margins ranged from 5% to 39.8% after NAC versus 13.1%-46% for primary BCS[36]. These percentages were

based on ten studies describing involved margins with or without NAC, but a clear comparison between these studies was not possible due to variation in terminology and variation amongst patient groups. Because of the nationwide character of our study in which all patients treated with invasive breast cancer are included, a 6,9% involved margin rate for BCS after NAC and a 3,3% involved margin rate for primary BCS is a reliable baseline for the quality of care in the Netherlands nowadays.

An important result of this nationwide data is that BCS after NAC leads to equal surgical outcomes for cT2 and improved outcomes for cT3 invasive breast cancer compared to primary BCS. Boughey et al. already described in 2006 using data from 1998 to 2005, that NAC reduces the volume of tissue excised in patients with T2 and T3 breast cancer treated with BCS, without an increase in rates of reexcision[37]. Ever since, improvements of targeted therapies to achieve a pathologic complete response (pCR) in combination with improvements in the identification of the original tumour location have led to more BCS after NAC with less involved invasive margins and a lower re-operation rates[9-12,22].

Our multivariable analyses detailed important prognostic factors associated with a higher risk of involved invasive margins for patients who will receive BCS after NAC: lobular invasive breast cancer, an increasing clinical tumour stage and a hormone receptor positive receptor status. A decreased feasibility for successful BCS has been described in the setting of lobular histology, multicentricity and diffuse calcifications noted on preoperative mammography[38]. And, it is known that HR-positive subtypes are associated with the lowest rates of pathological complete response (pCR)[30]. Another interesting assumption made by Landscaper et al. is that cancer subtypes may have an independent association with a surgical outcome, reported that triple-negative patients not receiving NAC had the lowest reoperation rate. This result correlates with our findings that a positive hormone receptor status was clearly associated with involved invasive margins for cT3 tumours, with no difference between patients receiving NAC and patients receiving no NAC. Because larger tumour size and higher grade are characteristics commonly reported on triple negative patients and because NAC is the standard of care for many of these patients[39], this will have contributed to the lower rate of involved margins for cT3 invasive breast cancer patients treated with NAC as seen in our study. Moreover, it supports the biologic heterogeneity of invasive breast cancer with its own approach and expected surgical outcomes.

Unaddressed issues are recurrence rates and cosmetic outcomes for patients treated with BCS after NAC, which we were unable to investigate in this study. A strong association of improved long-term outcomes in patients with pCR compared to patients with residual invasive tumour at the time of surgery has been consistently reported by many groups[11,30,40,41]. However, the surrogacy of pCR as an endpoint for long-term clinical outcome has not been established[42]. Future analyses of randomized trials of targeted agents in homogeneous tumour subtypes will help elucidate whether there is a significant association between pCR and long-term outcomes. Cosmetic outcomes for NAC followed by BCS have only been reported in retrospectives studies and no conclusions can be drawn yet[43,44]. Several studies do describe a lower resected volume in patients treated with neoadjuvant therapy compared to adjuvant therapy, what potentially could lead to better cosmetic outcomes and an improved quality of life. Although we did not specify resection volumes and cosmetic outcome in this study, we emphasize the fact that follow-up on this subject is necessary and of major impact in delivering quality care to patients. A poor cosmetic outcome after BCS should be avoided at any time. Work has been established to link patient reported outcome measurements (PROMS) to clinical data of patients treated with BCS after NAC and will eventually show the patients' satisfaction and long term cosmetic outcomes. This information will be of great value empowering patients to be effective advocates for their health, and that they can make informed decisions in light of it.

To our knowledge, this is one of the largest studies on a nationwide level demonstrating a trend of more BCS after NAC in relation to surgical outcomes. However, our study is limited by the retrospective nature and incomplete information on tumour response after NAC. Also, we were unable to retrospectively determine the percentage of patients eligible for BCS at the time of diagnosis.

CONCLUSION

The increasing implementation of NAC have led to an increase in 'BCS after NAC' in the Netherlands between 2011 and 2016. Moreover, this nationwide data confirms that BCS after NAC results in equal surgical outcomes for cT2 and improved surgical outcomes for cT3 invasive breast cancer compared to primary BCS. In view of the trend towards de-escalation of surgical treatment in selected patients with excellent pathologic response, these promising results confirm that clinicians are increasingly able to perform 'BCS after NAC' while maintaining good surgical outcomes.

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Table A. Clinical-pathological and hospital characteristics of cT1-4M0 breast cancer patients (N=36.475) who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).

	BCS		BCS after NAC		
	(N=32.305)		(N=4170)		
Year of incidence					*<0,005*
2012	6118	19%	424	*10%*	
2013	6466	20%	626	*15%*	
2014	6720	21%	836	*20%*	
2015	6368	20%	1086	*26%*	
2016	6633	21%	1198	*29%*	
Age					*<0,005*
<40	617	*2%*	395	*9%*	
40-50	3308	*10%*	1307	*31%*	
50-60	8787	*27%*	1462	*35%*	
60-70	10852	*34%*	872	*21%*	
70-100	8735	*27%*	132	*3%*	
Histologic subtype					*<0,005*
Ductal	26920	90%	3633	*92%*	
Lobular	2979	10%	331	*8%*	
DCIS component					*<0,005*
No	16487	*51%*	2684	*64%*	
Yes	15818	*49%*	1486	*36%*	
Clinical tumor stage					*<0,005*
cT1	26003	*80%*	706	*17%*	
cT2	6156	*19%*	2948	*71%*	
cT3	92	*0%*	442	*11%*	
cT4	54	*0%*	74	*2%*	
Clinical nodal stage					*<0,005*
cN0	30678	95%	1976	*47%*	
cN1	1558	5%	1921	*46%*	
cN2	42	0%	80	*2%*	
cN3	26	0%	192	*5%*	
Hormone receptor status					*<0,005*
Triple -	2793	*9%*	890	*22%*	
HR -, HER2+	707	*2%*	338	*8%*	
HR +, HER2+	2113	*7%*	610	*15%*	
HR +, HER2-	25000	*82%*	2237	*55%*	
Type of hospital					*<0,005*
General-	12635	*39%*	1356	*33%*	
Teaching-	17019	*53%*	1987	*48%*	
Academic-	2651	*8%*	827	*20%*	
Hospital surgical volume					*<0,005*
< 150	8635	*27%*	1043	*25%*	
150-300	12202	*38%*	1557	*37%*	
> 300	11163	*35%*	1562	*38%*	

Table B. Clinical-pathological and hospital characteristics associated with tumour free margins in cT1-4M0 breast cancer patients who have received breast conserving surgery after neoadjuvant chemotherapy (N= 4116).

	No involved margins (N=3835)		Involved margins (N=281)		
Year of incidence					*0,823*
2012	395	*94%*	25	*6%*	
2013	567	*93%*	43	*7%*	
2014	777	*94%*	52	*6%*	
2015	1004	*93%*	74	*7%*	
2016	1092	*93%*	87	*7%*	
Age					*0,017*
<40	377	*96%*	14	*4%*	
40-50	1203	*93%*	86	*7%*	
50-60	1337	*93%*	108	*7%*	
60-70	791	*92%*	68	*8%*	
70-100	126	*97%*	4	*3%*	
Histologic subtype					*<0,005*
Ductal	3419	*95%*	169	*5%*	
Lobular	239	*73%*	87	*27%*	
DCIS component					*0,606*
No	2473	*93%*	177	*7%*	
Yes	1362	*93%*	104	*7%*	
Clinical tumor stage					*<0,005*
cT1	672	*96%*	27	*4%*	
cT2	2731	*94%*	177	*6%*	
cT3	367	*84%*	68	*16%*	
cT4	65	*88%*	9	*12%*	
Clinical nodal stage					*0,024*
cN0	1837	*94%*	113	*6%*	
cN1	1752	*92%*	145	*8%*	
cN2	69	*87%*	10	*13%*	
cN3	176	*93%*	13	*7%*	
Hormone receptor status					*<0,005*
Triple -	865	*98%*	16	*2%*	
HR -, HER2+	333	*99%*	3	*1%*	
HR +, HER2+	590	*98%*	15	*2%*	
HR +, HER2-	1958	*89%*	244	*11%*	
Type of hospital					*<0,005*
General-	1242	*93%*	90	*7%*	
Teaching-	1855	*94%*	113	*6%*	
Academic-	738	*90%*	78	*10%*	
Hospital surgical volume					*0,672*
< 150	950	*93%*	74	*7%*	
150-300	1438	*94%*	98	*6%*	
> 300	1440	*93%*	108	*7%*	

CHAPTER 6

Trends on Axillary Surgery in Nondistant Metastatic Breast Cancer Patients Treated Between 2011 and 2015. A Dutch Population-based Study in the ACOSOG-Z0011 and AMAROS Era.

P.E.R. Spronk[§]
I.G.M. Poodt[§]
G. Vugts
T. van Dalen
M.T. F. D. Vrancken Peeters
M.L. Rots
A. Kuijer
G.A.P. Nieuwenhuijzen
R. Schipper
[§] both authors equally contributed to this article

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ABSTRACT

Objectives: To evaluate patterns of care in axillary surgery for Dutch clinical T1-4N0M0 (cT1-4N0M0) breast cancer patients and to assess the effect of the American College for Surgeons Oncology Group (ACOSOG)-Z0011 and After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial on axillary surgery patterns in Dutch cT1-2N0M0 sentinel node positive breast cancer patients.

Background: Since publication of the ACOSOG-Z0011 and AMAROS trial, omitting a completion axillary lymph node dissection (cALND) in sentinel node positive breast cancer patients is proposed in selected patients.

Methods: Data were obtained from the nationwide Nationaal Borstkanker Overleg Nederland breast cancer audit. Descriptive analyses were used to demonstrate trends in axillary surgery. Multivariable logistic regression analyses were used to identify factors associated with the omission of cALND in cT1-2N0M0 sentinel node-positive breast cancer patients.

Results: Between 2011 and 2015 in cT1-4N0M0 breast cancer patients, the use of sentinel lymph node biopsy as definitive axillary staging increased from 72% to 93%, and (c)ALND as definitive axillary staging decreased from 24% to 6% (P<0.001). The use of cALND decreased from 75% to 17% in cT1-2N0 sentinel node-positive patients (P<0.001). Earlier year of diagnosis, lower age, primary mastectomy, invasive lobular subtype, increasing tumor grade, and treatment in a nonteaching hospital were associated with a lower probability of omitting cALND (P<0.001).

Conclusions: This study shows a trend towards less extensive axillary surgery in Dutch cT1-T4N0M0 breast cancer patients; illustrated by an overall increase of sentinel lymph node biopsy and decrease in cALND. Despite this trend, particularly noticed in cT1-2N0 sentinel node-positive patients after publication of the ACOSOG-Z0011 and AMAROS trial, variations in patterns of care in axillary surgery are still present.

INTRODUCTION

Axillary lymph node management in breast cancer patients has changed dramatically during past decades.[1] Previously, performing an axillary lymph node dissection (ALND) was the standard of care for all nonmetastatic breast cancer patients. In the early 90s, sentinel lymph node biopsy (SLNB) was introduced as an accurate and less invasive axillary staging procedure, omitting the need for ALND in cT1-2N0M0 sentinel lymph node-negative breast cancer patients.[2,3] Despite, only small studies investigated accuracy of SLNB in cT3 sentinel lymph node-negative breast cancer patients, SLNB is also widely used in this group of patients.[4,5] In the early years after the introduction of SLNB, a completion ALND (cALND) was indicated in all patients with a positive sentinel lymph node.[6]

The additional value of cALND was first questioned in 2 randomized controlled trials—the American College for Surgeons Oncology Group (ACOSOG)-Z0011 trial and the After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial.[7,8] In the ACOSOG-Z0011 (accrual 1999–2004, published 2011), cT1- 2N0M0 breast cancer patients with 1 to 2 positive sentinel lymph nodes treated with breast-conserving therapy followed by whole breast radiotherapy were randomized between a cALND or no further axillary treatment.[7] Ten years cumulative incidence of ipsilateral axillary recurrences was 0.5% in the ALND group and 1.5% in the SLNB-alone group, with no significant difference in locoregional recurrence-free survival.[9]

The AMAROS trial (accrual 2001–2010, published 2014) evaluated whether regional control was comparable between cALND and axillary radiation therapy in cT1-2N0M0 breast cancer patients with 1 to 2 (and 5% >2) positive sentinel lymph nodes, treated with breast-conserving therapy, including whole breast radiotherapy or mastectomy with or without radiotherapy to the chest wall. There was no significant difference in the 5-year axillary recurrence rate between patients treated with cALND or axillary radiotherapy; 0.43% versus 1.19%. Axillary radiotherapy was associated with significantly less morbidity.[8] The AMAROS results indicated that in case of a positive sentinel node, both cALND and axillary radiotherapy provide excellent and comparable axillary control disease-free and overall survival for patients with cT1-2N0M0 primary breast cancer.

The first presentation of results of the ACOSOG-Z0011 in 2011 generated great debate under physicians. Some argued that the results should be considered unreliable since patients' accrual was discontinued before the foreseen number of patients was included. In addition, questions were raised regarding the selection of a favorable subgroup of patients; not all patients were treated with whole-breast radiotherapy as planned and lack of consistent documentation of radiation fields.[10–14] The safety of omitting cALND in sentinel node-positive breast cancer patients was questioned and resulted in hesitations to implement axillary lymph node-conserving treatment. This is illustrated by the 2012 Dutch Breast Cancer Guideline, merely suggesting omission of cALND in cT1-2N0M0 breast cancer patients with a maximum of 2 positive sentinel nodes treated with breast-conserving treatment and adjuvant systemic therapy. Based on previous literature and preliminary experience with the AMAROS trial, this guideline also suggested that axillary irradiation could serve as an alternative to cALND in sentinel node-positive patients for whom treatment of the axillary was considered necessary.[15]

The first aim of this study was to demonstrate patterns of care in axillary surgery for all Dutch cT1-4N0M0 breast cancer patients diagnosed between 2011 and 2015. The second aim was to evaluate the effects of the ACOSOG Z0011 and AMAROS trials in Dutch daily clinical practice. Furthermore, this study identified patient, tumor, and hospital-related factors associated with axillary surgery in cT1-2N0M0 sentinel node-positive breast cancer patients.

METHODS

Data were obtained from the Dutch Nationaal Borstkanker Overleg Nederland Breast Cancer Audit (NBCA). The NBCA is a multidisciplinary nationwide registry of all diagnostic and treatment modalities of patients who are surgically treated for breast cancer in the Netherlands since 2011. It is facilitated by the Comprehensive Cancer Center Netherlands (IKNL) and the Dutch Institute for Clinical Auditing (DICA). Data are registered directly by the hospital itself or by IKNL data managers. The quality of the Dutch Cancer registry is high and data completeness is estimated to be at least 95%.[16]

Patients and Hospitals

The current study sample consisted of Dutch patients diagnosed with cT1-4N0M0 invasive breast cancer between January 2011 and October 2015. Patients with the following criteria were excluded: <18 years of age, those who received neoadjuvant systemic therapy, had any prior surgery of the breast or those of whom information on the axillary surgery was indistinct. Data from 85 different Dutch hospitals (9 academic, 38 teaching, and 38 general nonteaching hospitals) were included. Not every hospital is represented in each year due to mergers or acquisitions, resulting in 82 entities in 2011 versus 71 entities in 2015.

Construction of Variables

Hospitals were divided into groups according to their teaching status (general nonteaching, teaching, academic) and surgical hospital volume. Teaching and academic hospitals both provide in-house surgical training to residents, with distinction that academic hospitals are directly connected with a medical faculty of a university. Specialized oncologic hospitals were classified as academic hospitals. Hospital volume was defined as the number of patients who underwent breast cancer surgery per year. Hospitals were divided into low volume (<150 resections), middle volume (150–300 resections), and high volume (>300 resections) on average per year. The cut-off points chosen were based on those reported in a publication of Eusoma, the European Society of Breast Cancer Specialist,[17] and those reported in an article from Greenup et al.[18] A positive sentinel node included micrometastases and macrometastases; isolated tumor cells were considered as sentinel node-negative.

Since the NBCA did not register the radiation fields, we could not describe whether or not a patient received radiotherapy on the breast (partial or whole) and/or axilla and/or other regions. Furthermore, we did not have access to information on adjuvant hormonal therapy in all patients.

Statistical Analyses

Descriptive analyses were used to report on the trends in axillary surgery for all cT1-4N0M0 breast cancer patients. The outcome of interest was the definitive surgical axillary treatment and was divided into 4 groups: no surgical nodal staging; SLNB–negative; SLNB-positive, no cALND; (c)ALND. The fourth group consisted of patients who were treated with SLNB followed by cALND, and of patients treated with ALND directly.

Univariable and multivariable logistic regression analyses were used to determine the probability to omit a cALND in selected cT1-2N0M0 sentinel node-positive breast cancer patients. A P value of <0.05 was considered statistically significant. Data analysis was performed using SPSS version 24 (SPSS Inc, Chicago, IL).

RESULTS

Patients

In all, 44,902 patients were diagnosed with cT1-4N0M0 invasive breast cancer between January 2011 and October 2015, and registered in the NBCA. Exclusion of patients <18 years of age (n=14), those who received neoadjuvant systemic therapy (n=3333), had any prior surgery of the breast (n=4014), or those of whom information on the axillary surgery was indistinct (n=21), resulted in a study population of 37,520 patients (see flowchart of exclusion criteria, supplement). Median age was 63 years (19-98); 5335 patients (12%) were older than 75 years. Most of the patients were diagnosed with a cT1 tumor (72%, n=27,066), whereas 26% of the patients were diagnosed with a cT2 tumor (n=9575), 2% with a cT3 tumor (n=743), and 0.4% with a cT4 tumor (n=136) (see **supplemental Table A**, which demonstrates the clinical-pathological and hospital characteristics of all cT1-4N0M0 patients [n= 37,520] and percentages of an ALND).

Trends in Axillary Surgery in cT1-4N0M0 Breast Cancer Patients

In 2011, 92% of all cT1-4N0M0 breast cancer patients were staged using SLNB, increasing to 98% in 2015. According to the tumor stage the use of SLNB increased from 93% to 98% in cT1 tumors, from 92% to 98% in cT2 tumors, from 68% to 88% in cT3 tumors, and from 29% to 70% in cT4 tumors (**Fig. 1**).

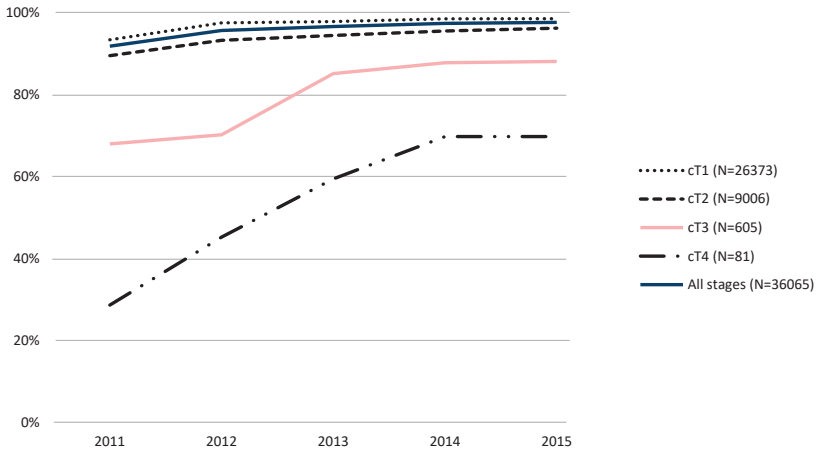

Figure 1. Trend in percentages of sentinel lymph node biopsy (SLNB) in cT1-4N0M0 breast cancer patients in the Netherlands from 2011 to 2015 according to clinical tumor (cT) stage.

In case of a positive SLNB within the group of cT1-4N0M0 breast cancer patients (n=8539), the use of a cALND decreased between 2011 and 2015. As shown in Fig. 2, this decline was noticed in all clinical tumor stages of disease: from 74% to 13% for cT1 (n=5159) tumors and 77% to 23% for cT2 tumors (n=3032). Of note, also in cT3 and cT4 tumors, a decreasing trend was observed in the use of a cALND: from 88% to 27% in cT3 tumors (n=307) and from 50% to 17% in cT4 tumors (n=41), respectively.

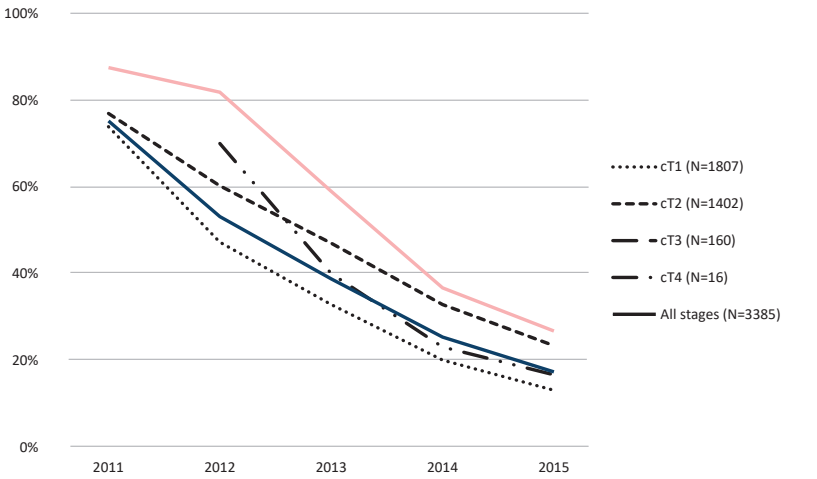

Figure 2. Trend in percentages of complementary axillary lymph node dissection (cALND) in cT1-4N0M0 sentinel node positive breast cancer patients in the Netherlands from 2011 to 2015 according to clinical tumor (cT) stage.

Figure 3 shows the percentage of patients according to their definitive axillary staging in the period 2011 to 2015. Hence, these are percentages of the complete group of patients diagnosed with cT1-4N0M0 invasive breast cancer (n=37,520) divided into the following groups: no axillary staging (n=954), SLNB (negative = 27,200 or positive = 5154) without an ALND and (c)ALND (n=4572). Obviously, the proportion of patients with a positive SLNB as definitive axillary staging procedure increased from 6% (n=282) in 2011 to 18% (n=1411) in 2015 ($P < 0.001$). In these cT1-4N0M0 sentinel node-positive breast cancer patients, a cALND was omitted.

Rarely, in a proportion of patients with a negative SLNB (n= 27,526), a cALND was performed (1%, n=326). This percentage remained unchanged over the years and was not associated with either age or clinical tumor stage. Apart from this, 861 out of

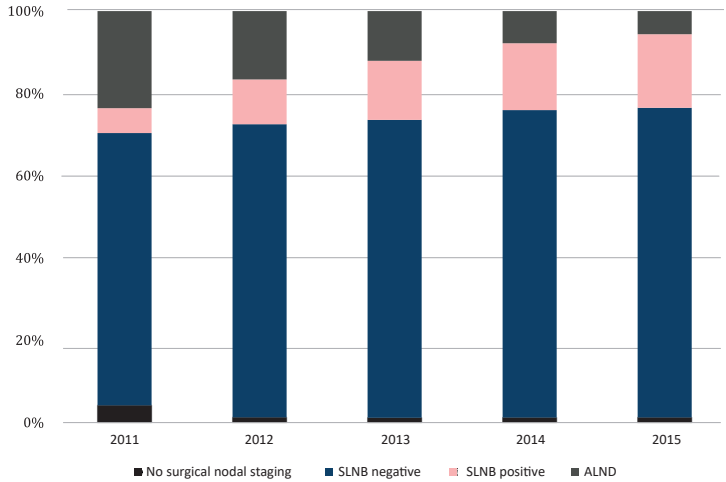

Figure 3. Trends in the definitive axillary staging in cT1-4N0M0 breast cancer patients in the Netherlands from 2011 to 2015.

all 37,520 (2.3%) cT1-4N0M0 breast cancer patients received ALND directly, without previous axillary staging. Overall, percentages of SLNB as definitive axillary staging increased from 72% in 2011 to 93% in 2015, and percentages of (c)ALND as definitive axillary staging declined from 24% in 2011 to 6% in 2015 (P<0.001).

Trends in Axillary Surgery in cT1-2N0M0 Sentinel Node-positive Breast Cancer Patients

A subgroup analysis was performed in cT1-2N0M0 breast cancer patients with 1 to 2 (and 1.8% >2) positive sentinel lymph nodes; a group comparable with the ACOSOG-Z0011 and AMAROS trial population. A total of 8191 out of 36,641 cT1-2N0M0 patients were sentinel node-positive with a median age of 60 years (22–96).

The clinical, pathological, and hospital characteristics of this population are shown in Table 1. Most of these patients underwent breastconserving surgery (61%, n=4959) and were classified with a ductal, unifocal, hormone receptor-positive, and human epidermal growth receptor (HER)2-negative breast tumor. The majority (84%, n=5939) of the cT1-2N0M0 sentinel node-positive patients received radiotherapy on any region and 62% (n=4646) of the patients received adjuvant chemotherapy.

Table 1. Clinical- pathological and hospital characteristics of cT1-2N0M0 sentinel node positive patients (N=8191) and percentages of complementary axillary lymph node dissection (cALND), 2011 -2015.

	N	cALND		*p*-Value
Incidence year				
2011	1111	833	*75%*	*<0.001*
2012	1815	947	*52%*	
2013	1905	723	*38%*	
2014	1730	430	*25%*	
2015	1630	276	*17%*	
Age				
<40	326	183	*56%*	*<0.001*
40-50	1309	624	*48%*	
50-75	5394	2035	*38%*	
75+	1162	367	*32%*	
Histologic subtype				
ductal	7112	2721	*38%*	*<0.001*
lobular	1079	488	*45%*	
Clinical tumor stage				
cT1	5159	1807	*35%*	*<0.001*
cT2	3032	1402	*46%*	
Multifocality				
unifocal	6893	2583	*37%*	*<0.001*
multifocal	1298	626	*48%*	
Receptor status				
triple -	456	225	*49%*	*<0.001*
HR -, Her2+	212	102	*48%*	
HR+, Her2+	650	267	*41%*	
HR+, Her2-	6361	2374	*37%*	
unknown	512	241	*47%*	
Grade				
I	1753	586	*33%*	*<0.001*
II	4217	1634	*39%*	
III	2101	933	*44%*	
unknown	120	56	*47%*	
Initial surgery				
mastectomy	3232	1691	*52%*	*<0.001*
breast conserving treatment (BCT)	4959	1518	*31%*	
Radiotherapy (on any region)				
no	1138	672	*59%*	*<0.001*
yes	5939	1760	*30%*	
Unknown	785	554	*71%*	

Table 1. (continued)

	N	cALND		*p*-Value
Adjuvant chemotherapy				
no	2937	781	*27%*	*<0.001*
yes	4646	2135	*46%*	
unknown	607	293	48%	
Type of hospital				
general non-teaching	2993	1353	*45%*	*<0.001*
teaching hospital	4582	1684	*37%*	
academic	616	172	*28%*	
Hospital surgical volume				
<150	2450	1076	*44%*	*<0.001*
150-300	3060	1113	*36%*	
>300	1988	732	*37%*	
unknown	693	288	*42%*	

cALND complementary axillary lymph node dissection, *cT* clinical tumor, *HR* hormone receptor, *Her2* human epidermal growth receptor 2

As shown in Table 1, within this subgroup of cT1-2N0M0 sentinel node-positive patients, the performance of a cALND decreased from 75% in 2011 (ACOZOG-Z0011 published), to 25% in 2014 (AMOROS published) and 17% in 2015. In cT1-2N0M0 sentinel node-positive breast cancer patients, younger patients were more likely to receive a cALND. Over time, the rate of cALND for patients aged <40 decreased from 89.6% in 2011 to 61.8%, 47.0%, 37.7%, and 39.6% in 2012, 2013, 2014, and 2015, respectively. The rate of cALND for patients aged 50 to 75 decreased from 76.4% in 2011 to 51.1%, 37.1%, 23.3%, and 15.9% in 2012, 2013, 2014, and 2015, respectively.

Regarding the receptor status, triple negative patients had a higher probability in receiving cALND. Over time, the rate of cALND in triple negative patients declined from 79.0% in 2011 to 56.6%, 50.0%, 33.7%, and 25.3%in 2012, 2013, 2014, and 2015, respectively.

In case of breast-conserving therapy, a cALND was omitted more often (69%) compared with mastectomy (48%) (P<0.001). **Figure 4** shows the type of primary surgery of cT1-2N0M0 sentinel node-positive patients treated with a cALND from 2011 to 2015. The proportion of patients receiving cALND declined for both types of surgery over the years, but notable is the slower adaption of omitting cALND in the mastectomy group.

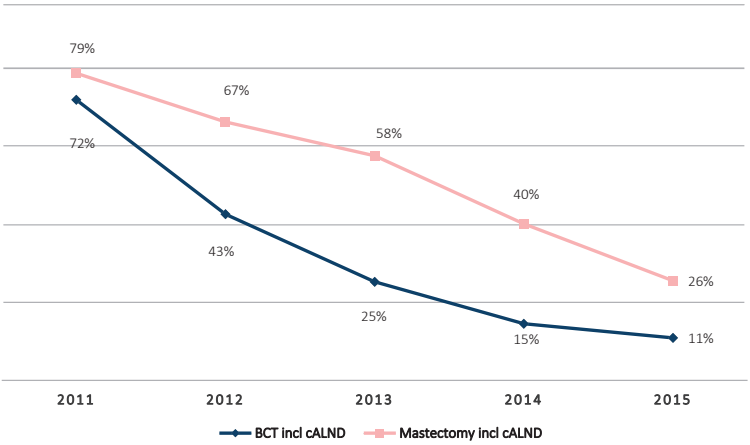

Figure 4. Percentages of cT1-2N0M0 sentinel node positive breast cancer patients in which a complementary axillary lymph node dissection (cALND) was performed; breast conserving therapy (BCT) versus mastectomy.

Prognostic Factors Omitting a cALND in cT1- 2N0M0 Sentinel Node-positive Patients

A multivariable logistic regression analysis was used to determine independent predictors in omitting cALND (Table 2). Apart from an earlier year of diagnosis, lower age and patients being treated with mastectomy, also invasive lobular subtype, increasing tumor grade and being treated in a general nonteaching hospital were independently associated with a lower probability in omitting cALND (all P<0.001). Hospital surgical volume and receptor status were not independently associated with omitting cALND in multivariable analysis.

Table 2. Univariable and multivariable analyses for the performance of complementary axillary lymph node dissection (cALND) among cT1-2N0M0 sentinel node positive patients (N=8191), 2011 -2015.

	Univariable			Multivariable		
	Odds	**CI Interval**	***p*-Value**	**Odds**	**CI Interval**	***p*-Value**
Incidence year						
2011	ref.		*<0.001*	ref.		*<0.001*
2012	0,364	(0,309 - 0,429)		0,359	(0,297 - 0,435)	
2013	0,204	(0,173 - 0,241)		0,206	(0,17 - 0,249)	
2014	0,111	(0,093 - 0,132)		0,092	(0,075 - 0,113)	
2015	0,068	(0,056 - 0,082)		0,059	(0,047 - 0,073)	

Table 2. (continued)

	Univariable			Multivariable		
	Odds	**CI Interval**	***p*-Value**	**Odds**	**CI Interval**	***p*-Value**
Age						
<40	ref.		*<0.001*	ref.		*<0.001*
40-50	0,712	(0,564 - 0,918)		0,723	(0,535 - 0,976	
50-75	0,473	(0,383 - 0,602)		0,638	(0,482 - 0,845)	
75+	0,361	(0,284 - 0,464)		0,297	(0,216 - 0,407)	
Histologic subtype						
ductal	ref.		*<0.001*	ref.		*0,023*
lobular	1,33	(1,171 - 1,516)		1,214	(1,027 - 1,433)	
Clinical tumor stage						
cT1	ref.		*<0.001*	ref.		*<0.001*
cT2	1,596	(1,456 - 1,748)		1,303	(1,156 - 1,469)	
Multifocality						
unifocal	ref.		*<0.001*	ref.		*0,035*
multifocal	1,554	(1,38 - 1,751)		1,18	(1,012 - 1,377)	
Receptor status						
triple -	ref.		*<0.001*	ref.		*0,185*
HR -, Her2+	0,952	(0,687 - 1,319)		0,822	(0,557 - 1,213)	
HR+, Her2+	0,716	(0,562 - 0,911)		0,732	(0,548 - 0,978)	
HR+, Her2-	0,611	(0,505 - 0,74)		0,786	(0,617 - 1,001)	
Grade						
I	ref.		*<0.001*	ref.		*0,012*
II	1,968	(1,863 - 2,078)		1,052	(0,91 - 1,216)	
III	2,567	(2,425 - 2,717)		1,271	(1,068 - 1,513)	
Initial surgery						
mastectomy	ref.		*<0.001*	ref.		*<0.001*
nreast conserving treatment(BCT)	0,402	(0,367 - 0,441)		0,335	(0,295 - 0,381)	
Type of hospital						
general non-teaching	ref.		*<0.001*	ref.		*<0.001*
teaching hospital	0,704	(0,641 - 0,774)		0,664	(0,566 - 0,779)	
academic	0,47	(0,388 - 0,568)		0,335	(0,263 - 0,426)	
Hospital surgical volume						
<150	ref.		*<0.001*	ref.		*0,327*
150-300	0,913	(0,876 - 0,953)		1,125	(0,963 - 1,315)	
>300	0,861	(0,822 - 0,903)		1,113	(0,926 - 1,337)	

CI confidence interval, *Ref* reference, *cT* clinical tumor, *HR* hormone receptor, *Her2* human epidermal growth receptor 2

DISCUSSION

This study showed a trend towards less extensive axillary surgery in Dutch cT1-T4N0M0 breast cancer patients in the ACOSOG-Z0011 and AMAROS era. Particularly in cT1-T2N0M0 sentinel node-positive invasive breast cancer patients, the performance of a cALND decreased from 75% in 2011 to 17% in 2015. The downward trend observed in the use of cALND in cT1- 2N0 sentinel node-positive breast cancer patients reflects the implementation of the study concept of the ACOSOG-Z0011 and AMAROS trials in the Netherlands. In these patients, axillary surgery varied between patients treated with breast-conserving therapy and mastectomy. In 2011, the percentage of patients without a cALND was higher in the breast-conserving therapy group (28%) compared with the mastectomy group (21%). Only a small percentage of patients (0% in the ACOSOG-Z0011 and 18% in the AMAROS trial) were treated with mastectomy, which could be a reason why omitting cALND in mastectomy patients was less likely adopted by surgeons.

As expected, due to the presentation of the results of the ACOSOG-Z0011 trial, a reduction in the number of cALND performed in patients treated with breast-conserving therapy was observed. While the results of the AMAROS trial were presented in 2014, a reduction in the percentage of cALND in patients treated with mastectomy was already observed in 2013. This may reflect the confidence of physicians in the concept that not every positive axillary sentinel lymph node will develop into clinical detectable axillary disease.[7,19]

In some patients, physicians were still reluctant to omit cALND. As reported in this study, the probability of omitting cALND decreased when patients were younger (<40 years), were treated in a general nonteaching hospital, or had more aggressive tumor biology. The relation of younger age (<40 years) to higher cALND rates may reflect the hypothesis that treatment of the axilla should be more aggressive in younger patients to optimize overall survival. However, the prognostic relevance of young age on the occurrence of regional recurrences is controversial.[20–22] Physicians may extrapolate the higher risk of young patients to develop a local recurrence to the regional recurrence risk. Indeed, the occurrence of a local recurrence affects the overall survival of young patients.[21,23–25]

On the contrary, the ACOSOG-Z0011 10-year follow-up data showed that the number of regional recurrence is very low in both the ALND group (0.5%) and the SLNB-only group (1.5%), and no association of young age (<50 years) with loco-regional recurrences was observed.[9] Hence, it does not seem justified to be reluctant to omit a cALND based only on the age of the patient. This study reported that triple negative breast cancer patients with a positive SLNB were more likely to receive a cALND compared with hormone receptor-positive patients. This practice may be based on the criticism that in the ACOSOG-Z0011, only small numbers of patients with triple negative breast cancer were included and thus the results were not applicable for triple negative patients.[26,27] However, several studies do not support such an aggressive approach. Firstly, van Roozendaal et al questioned in their study whether triple negative patients with a clinically T1-2N0 status were more at risk for regional recurrences. Their 5-year follow-up showed a regional and distant recurrence rate of 2.9% and 12.2%, respectively. It was concluded in this study that triple negative tumors rarely recur regionally and that their disease-free survival was more threatened by distant recurrence.[28] Secondly, being at high risk to develop distant metastasis does not necessarily mean being at high risk for axillary nodal recurrence.[26] Thirdly, a recent follow-up study on the ACOSOG-Z0011 eligible patients was publicized. It was reported that after a median follow-up of 31 months, high-risk patients (ie, triple negative tumors, HER2-positive tumors, and age <50 years) compared with average-risk patients had the same risk of regional recurrence, but a higher risk of developing distant metastasis.[27] Hence, although longer follow-up data are preferable, it does not seem justifiable to perform a cALND based on receptor status only.

We evaluated a significant variation in omitting cALND between different types of hospitals, revealing the presence of early and late adopters. While the first hospitals started omitting cALND in 2011, other hospitals still performed this procedure in 2015, as has been reported by other authors.[29–31] van Steenbergen et al[29] evaluated in 2010 the implementation of SLNB in the Netherlands and showed that general nonteaching hospitals were late adopters of the SLNB procedure by performing ALND more frequently than other hospitals. This variation might be explained by the degree of dedication of the multidisciplinary breast cancer treatment teams within a hospital or whether a radiotherapy center was located nearby the treating hospital. Within the current study, there was no information about these possible influencing factors which

should be evaluated in future studies. This variation is not favorable, but unfortunately the implementation process following the presentation of evidence-based studies and guidelines is seldom monitored and reasons for nonadherence are largely unknown.

Another notable pattern of care was the downward trend of cALND in cT3-4N0M0 sentinel node-positive breast cancer patients, which was in line with the decreasing trend in cT1-2N0M0 sentinel node-positive breast cancer patients. No randomized trials have been published to justify less extensive axillary surgery in cT3-4N0M0 sentinel node-positive breast cancer patients. Nonetheless, the decreasing trend in the numbers of cALNDs performed in all tumor stadia might reflect the growing argument for less extensive surgery in the axilla of breast cancer patients.

In addition, this study revealed an increase in the use of SLNB, especially in cT3 and cT4 patients, from 68% to 87% and 29% to 70%, respectively. This increasing trend in the use of SLNB for nodal staging in breast cancer patients reflects the growing confidence in the concept of this procedure, even in patients with T3 and T4 tumors. The accuracy in performing SLNB in cT3 tumors seems to be comparable to T1 and T2 tumors according to the available literature. Although, the evidence supporting this practice is debatable, since only small studies were published.[4,5] No conclusive data are available on the accuracy of SLNB in cT4N0M0 breast cancer patients.

To our knowledge, this is the largest study demonstrating patterns of care of axillary surgery in breast cancer patients. It shows that trial results of the ACOSOG-Z0011 and AMAROS were progressively implemented in axillary treatment plans of breast cancer patients nowadays. Our study is limited by its retrospective nature and by incomplete information on radiation therapy and fields. Therefore, we could not explore the potential effect of radiation on the axilla. These considerations should be taken into account when discussing axillary treatment options. Excluding neoadjuvant treated patients could result in biased underuse of cALND through the omission of high-stage breast cancer patients who underwent neoadjuvant treatment. Despite the discussion on both trials, we observed a notable early adoption and increasing trend in omitting the use of cALND in sentinel nodepositive cT1-2N0M0 breast cancer patients, both treated with breast-conserving surgery and mastectomy.

CONCLUSIONS

This study shows a trend towards less extensive axillary surgery in Dutch cT1-T4N0M0 breast cancer patients, illustrated by an overall increase of SLNB and decrease in cALND. Despite this decreasing trend particularly noticed in cT1-2N0M0 sentinel nodepositive patients after the presentation of the ACOSOG-Z0011 and AMAROS trial, hospital-related variation in axillary surgery is still present. This emphasizes the need for a uniform implementation strategy after the publication of national guidelines which includes an education program for surgeons and patients, to minimize variations in patterns of care in oncologic breast cancer surgery.

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SUPPLEMENTAL

Table A. Clinical- pathological and hospital characteristics of all cT1-4N0M0 patients (N=37520) and percentages of an axillary lymph node dissection (ALND), 2011 -2015.

	N	ALND		*p*-Value
Incidence year				
2011	4663	1100	*24%*	*<0.001*
2012	8097	1346	*17%*	
2013	8507	1029	*12%*	
2014	8362	653	*8%*	
2015	7891	444	*6%*	
Age				
<40	1135	227	*20%*	*<0.001*
40-50	4615	806	*17%*	
50-75	26435	2770	*10%*	
75+	5335	769	*14%*	
Histologic subtype				
ductal	32804	3793	*12%*	*<0.001*
lobular	4716	779	*17%*	
Clinical tumor stage				
cT1	27066	2367	*9%*	*<0.001*
cT2	9575	1866	*19%*	
cT3	743	284	*38%*	
cT4	136	55	*40%*	
Multifocality				
unifocal	32919	3564	*11%*	*<0.001*
multifocal	4601	1008	*22%*	
Receptor status				
triple -	3323	376	*11%*	*<0.001*
HR -, Her2+	1024	160	*16%*	
HR+, Her2+	2686	356	*13%*	
HR+, Her2-	28159	3320	*12%*	
unknown	2328	360	*15%*	
Grade				
I	9797	818	*8%*	*<0.001*
II	17528	2298	*13%*	
III	9289	1369	*15%*	
unknown	904	87	*10%*	
Initial surgery				
mastectomy	11961	2719	*23%*	*<0.001*
breast conserving treatment (BCT)	25559	1853	*7%*	
Radiotherapy on any region				
no	6183	1014	*16%*	*<0.001*

Table A. (continued)

	N	ALND		*p*-Value
yes	26566	2373	*9%*	
unknown	3419	846	*25%*	
Adjuvant chemotherapy				
no	20958	1412	*7%*	*<0.001*
yes	12317	2670	*22%*	
unknown	4242	490	*12%*	
Type of hospital				
general non-teaching	13393	1971	*15%*	*<0.001*
teaching	21208	2372	*11%*	
academic	2919	229	*8%*	
Hospital surgical volume				
<150	11384	1584	*14%*	*<0.001*
150-300	13745	1606	*12%*	
>300	9175	989	*11%*	
unknown	3216	393	*12%*	

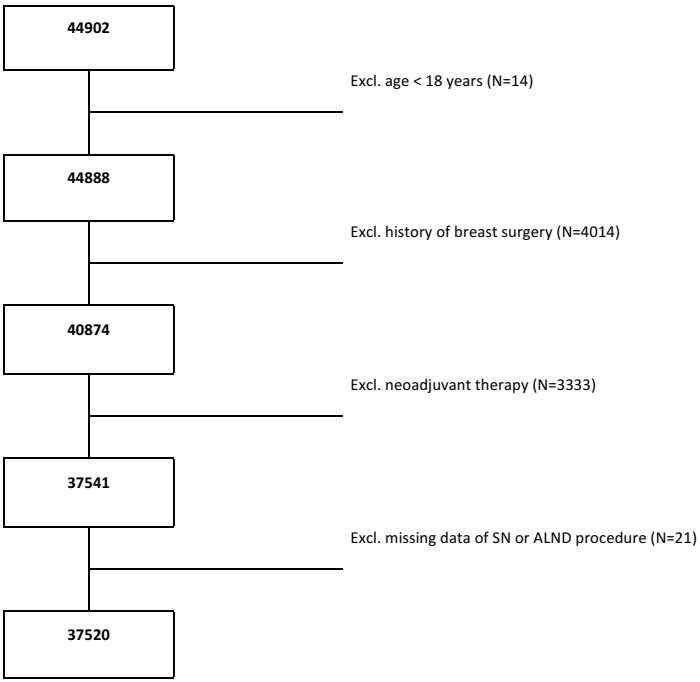

Figure A. Flowchart of exclusion criteria.
Excl exclusion, SN sentinel node, ALND axillary lymph node dissection

CHAPTER 7

How to improve patient safety and quality of care in breast implant surgery? First outcomes from the Dutch Breast Implant Registry (2015 – 2017)

P.E.R. Spronk
B.E. Becherer
J. Hommes
X.H.A. Keuter
D.A. Young-Afat
M.J. Hoornweg
M.W.J.M. Wouters
M.A.M. Mureau
H.A. Rakhorst

Submitted

ABSTRACT

Background: Although the use of breast implants is generally considered to be safe, breast implants are associated with short- and long-term complications. To evaluate and improve the quality of breast implant surgery, and increase our knowledge of implant performance, the national Dutch Breast Implant Registry (DBIR) was established in 2015. DBIR is one of the first up-and-running breast implant registries worldwide and follows an opt-out structure.

Objective: This article provides an overview of the first outcomes and experiences of the DBIR.

Methods: The national coverage of DBIR was studied, using data from the Dutch Health and Youth Care Inspectorate. For 2016 and 2017 the incidence rate of breast implants was calculated, and patient, device, and surgery characteristics were compared between cosmetic breast augmentations or reconstructive indications. Four infection control measures were selected to demonstrate the variation in the Dutch clinical practice.

Results: In 2016, 95% of the hospitals and 78% of the private clinics participated in DBIR. Between 2015 and 2017, a total of 15,049 patients and 30,541 breast implants were included. A minimum breast implant incidence rate of 1 woman per 1,691 women could be determined for 2017. The majority of devices was inserted for a cosmetic indication (85.2%). In general, patient, device, and surgery characteristics differed per indication group. Substantial variation was seen in the use of infection control measures (range 0-100%).

Conclusion: Preliminary results obtained from DBIR show high national participation rates and support further developments towards the improvement of breast implant surgery and patient safety.

INTRODUCTION

Since the introduction of breast implant surgery approximately six decades ago, numerous studies have evaluated the health effects and safety of breast implants.[1] These studies suggested that breast implants are to be considered safe. Nonetheless, a variety of surgical complications may occur following breast implant surgery, such as infection, implant rupture or deflation, late seroma, and capsular contracture.[2,3,4]

Recently, an association between Anaplastic Large Cell Lymphoma (ALCL) of the breast has been found.[5,6,7] Furthermore, the debate on possible associations between silicone exposure and various autoimmune diseases or connective tissue diseases continues (e.g., ASIA, an autoimmune/inflammatory syndrome induced by adjuvants)[8,9,10,11,12] Therefore, the outcomes of 'real world' data are becoming of increasing scientific and clinical importance to assess the effect of various intraoperative techniques and the use of different types of breast implants, while controlling for confounding factors adequately.[13,14]

In response to this, several countries have developed breast devices registries, among which the Dutch Breast Implant Registry (DBIR).[15,16,17,18,19,20] In April 2015, the DBIR started to register all patients undergoing breast implant surgery in the Netherlands (both implantations and explantations).[21] Currently, the audit provides hospitals and private clinics with weekly updated, benchmarked information on their performance. Additionally, the registry can be used as a track-and-trace system in case of an implant recall and identify patients who have the implant(s) of interest. DBIR follows an opt-out construct, which is unique compared to other breast implants registries worldwide.

Recent research has shown that the estimated prevalence of women with breast implants was 3,3% in the Netherlands in 2015.[5] However, incidence rates and further details on surgery techniques used, types of inserted devices, and national trends are not known yet. By using data of the DBIR, this study aims to provide more insight into the patient characteristics of women undergoing breast implant surgery in the Netherlands, the different types of inserted devices, and the nationwide variation in surgical techniques used.

METHODS

A: Registry Methods

Governance

The Dutch Breast Implant Registry (DBIR), founded in 2014, was an initiative of the Netherlands Society for Plastic Surgery (NVPC).[22] It provides an audit system for plastic surgeons on outcomes of breast implant surgery and serves as a track-and-trace system for breast implants. More information on the establishment, organization, and funding of the registry can be found in the paper of Rakhorst et al. and the annual report.[21,23]

Quality indicators

The primary purpose of the DBIR is to provide healthcare providers with reliable, benchmarked information on structure, process and outcome parameters. These quantitative measures cover different aspects of breast implant surgery: patient characteristics, information about intraoperative techniques, and short- and long-term outcomes of implants. A first set of quality indicators was defined by the DBIR group and external stakeholders (e.g., Dutch Health and Youth Care Inspectorate (IGJ), healthcare insurance companies, the Federation of hospitals, and patient advocates). For 2018, three quality indicators will be made publically transparent for all hospitals and private clinics performing breast implant surgery in the Netherlands: (1) Participation in the registry, (2) Percentage of registered breast implants compared to the actual inserted/explanted devices, and (3) Percentage of completely registered records.

Data collection

Registration in the DBIR is done using an internet-based program and data are stored at a central server.[24] The dataset consists of four levels: (1) General patient information (e.g. anonymized patient identification number, age), (2) Patient characteristics during surgery (e.g. date of surgery, ASA classification, smoking, Body Mass Index (BMI), (3) Surgery techniques on breast level (e.g. indication, incision site, flap cover, or when applicable the indication for revision), and (4) Implant characteristics (e.g. manufacturer, serial number, lot number, texture, fill, shape).

Data verification and participation rate

The quality of the DBIR database is evaluated on three levels: (1) National coverage: the participation of all Dutch hospitals and private clinics participating in breast implant surgery, (2) Completeness: the number of registered procedures versus the actual number of procedures performed at each center, and (3) Validity: the quality of the data compared to the electronic patient records in the hospitals.

In this study, the national coverage was assessed by comparing the number of institutions in DBIR to the number of eligible institutions known by the Dutch Health and Youth Care Inspectorate (IGJ).

No gold standard is known for the evaluation of completeness of the DBIR yet. By now, data from the industry is far from complete, and national insurance data does not include cosmetic procedures. Therefore, this could not be determined in the current study.

B: Study Methods

Patient selection

Per record (i.e., breast), information on the date of birth, date of surgery, type of surgery (insertion/ replacement/explantation only), and device type was minimally required to be eligible for analysis. The minimum incidence rate was calculated using the total number of women between 20 and 80 years of age in the Netherlands, in 2016 and 2017.[25]

For further analysis, all patients who had received a breast implant from the start of the DBIR on April, 1st 2015 until the end of the second complete registration year at December, 31st 2017, with a known indication (either reconstructive or cosmetic), were included. Patients who had received a tissue expander were excluded from the analysis. The population was divided into two cohorts: cosmetic and reconstructive. The cosmetic group included all patients with a breast augmentation. The reconstructive group included all patients with the following indication: reconstruction post (prophylactic) mastectomy, reconstruction for a benign condition or reconstruction for a congenital deformity. To identify differences between hospital/clinics, and to identify where improvement can be made, four examples of used infection control measures

were selected: glove change prior to implant handling, antiseptic rinse before insertion, the use of postoperative drains, and the use of prophylactic antibiotics.

Analyses

Differences in patient characteristics, device characteristics, and surgical techniques are described using percentages, means, and medians (depending on the distribution). Records with a missing indication (either cosmetic or reconstructive) are presented separately. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using Student's t-test. Nationwide variation in the use of the four selected operative techniques was calculated in percentages per hospital per year and is visualized by scatterplots including the national mean. All analyses were performed using SPSS version 24.0 (SPSS Inc Chicago, IL, USA).

RESULTS

Nationwide participation rate DBIR

In the first full registration year (2016), 101 institutions were included in DBIR, of which 73 hospitals and 28 private clinics. This means coverage of 95% of the hospitals, and 78% of the private clinics when compared to the number of the eligible institutions known by the Dutch Health and Youth Care Inspectorate (IGJ) (**Figure 1**).

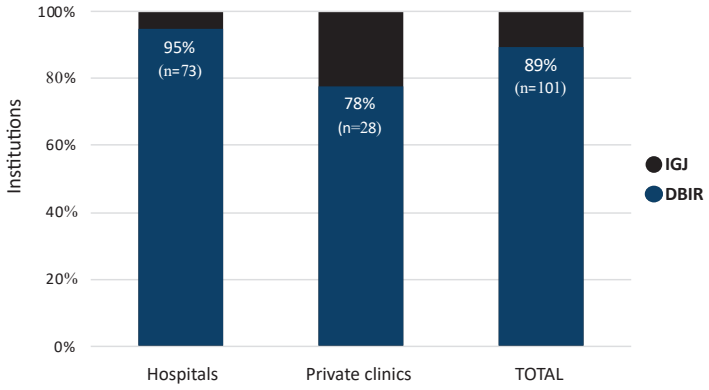

Figure 1. Nationwide participation rate DBIR (2016)
IGJ = Dutch Health & Youth Care Inspectorate.

Patients and minimum breast implantation incidence rates

In total, 48,493 records (i.e., breasts) have been registered with an operation date between the start of DBIR on April 1st, 2015 and December 31st, 2017, of which 48,026 (99.0%) were eligible for analysis (**Supplementary Figure 1)**. Of these, 41,919 were registered for the insertion of a breast implant. In 2016, 7,528 women received one or more permanent breast implant(s), accounting for a minimum incidence rate of one woman per 1,649 women. In 2017, the minimum incidence rate was one per 1,691 women (number of insertions: 7,391).

For further analysis, the indication for surgery needed to be known (either reconstructive or cosmetic). Therefore, 11,378 of the 41,919 records (27.1%) were excluded (36.8% in 2015, 32.8% in 2016, 15.1% in 2017). Eventually, 15,049 unique patients, 16,574 surgical procedures, and 30,541 breasts were included (**Figure 2**).

Patient characteristics

Patient characteristics per unique surgical procedure are presented in **Table 1**. In general, patients who had undergone a cosmetic breast augmentation were younger and had a lower ASA score compared with patients who received a breast reconstruction (all *p's* <0.001). Information on smoking and Body Mass Index (BMI) has been collected since September 2017. However, this information was missing in more than 5% of the records for both indications. **Supplementary Table 1a** contains all patient characteristics of the records in which no indication was specified.

Device characteristics

Between April 2015 and December 2017, 26,036 (85.2%) breast implants were inserted for a cosmetic breast augmentation, and 4,505 (14.8%) for a breast reconstruction. In both cosmetic and reconstructive indications, most devices had a textured shell (93.1% and 92.5%, respectively) with a silicone coating (96.3% and 91.6%, respectively), and with silicone filling (97.2% and 82.6%, respectively). Implants used in reconstructive indications were more often anatomically shaped instead of round (86.0% versus 30.6%, *p* <0.001). The median volume of inserted implants was higher in the reconstructive group (415cc, IQR 325-520) compared to the cosmetic group (350cc, IQR 300-405; *p* <0.001).

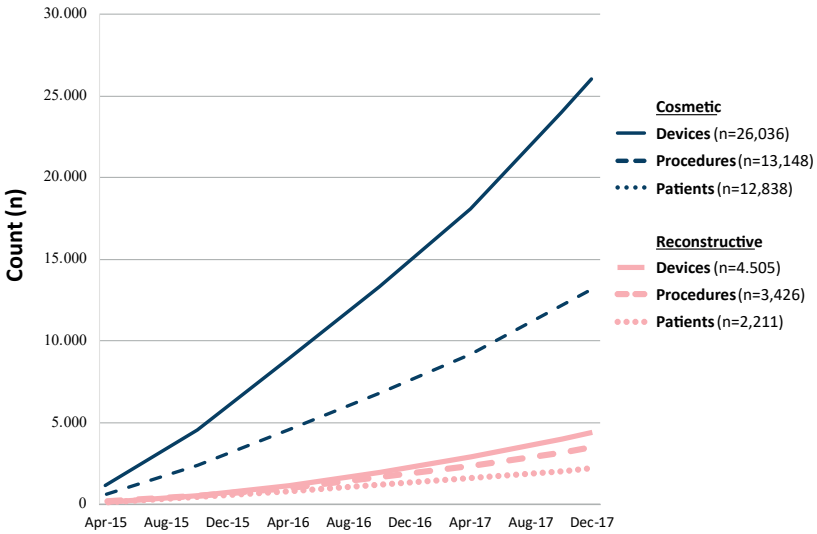

Figure 2. Cumulative number of registered patients, procedures and inserted breast implants (2015-2017)

Between 2016 and 2017, a decrease in the use of textured implants was seen for both indication groups (cosmetic: 96% to 89%, $p < 0.001$; reconstructive: 94% to 92%, $p = 0.04$) (**Figure 3)**. A similar trend was observed for the use of silicone coated devices (cosmetic: 98% to 95%, $p < 0.001$; reconstructive: 95% to 90%, $p < 0.001$). Furthermore, in the reconstructive group, an increase in the use of round implants (11% to 15%, $p < 0.001$) and silicone filled implants (78% to 85%, $p < 0.001$) was found. Characteristics of the 11,378 devices inserted for no specified indication are listed in **Supplementary Table 1b**.

Surgery characteristics

In the patients with a known indication for surgery, 26,036 (85.2%) breast implants were inserted for a cosmetic breast augmentation. Almost all cosmetic procedures were performed bilaterally (99.0%). Patients in the reconstructive group, however, more frequently underwent a unilateral procedure (52.1%, 2,349 of the 4,505 devices). As shown in **Table 2**, the incision site for a cosmetic breast augmentation was most frequently the inframammary fold (93.7%), while in reconstructive procedures the mastectomy scar was used in most cases (53.1%). For both cosmetic and reconstructive

Table 1. Patient characteristics per surgical procedure, presented on patient level (2015-2017)

	Cosmetic		Reconstructive		
	n	%	n	%	*P*
Patients[A]	13,148		3,426		
Age					<0.001
<30	6,227	47.4	205	6.0	
30-39	4,140	31.5	488	14.2	
40-49	1,794	13.6	876	25.6	
50-59	783	6.0	1,112	32.5	
>60	204	1.6	745	21.7	
ASA classification					<0.001
I	12,493	95.0	2,235	65.2	
II	532	4.0	1,040	30.4	
III-IV	30	0.2	90	2.6	
Unknown	*93*	*0.7*	*61*	*1.8*	
Smoking[B]					<0.001
Yes	218	10.5	61	9.9	
No	1,028	49.5	383	62.1	
Unknown	*830*	*40.0*	*173*	*28.0*	
BMI[B] (kg/m^2)					<0.001
<18.5	109	5.3	11	1.8	
18.5-25	1,529	73.7	273	44.2	
25 - 30	218	10.5	148	24.0	
>=30	32	1.5	55	8.9	
Unknown	*188*	*9.1*	*130*	*21.1*	

[A] *Patients per unique surgical procedure, no unique patients.*
[B] *Registered since September 2017. Percentages are calculated for a smaller population: n=2.076 (cosmetic), n=617 (reconstructive).*
ASA: American Society of Anesthesiologists. BMI: Body Mass Index.

indications, most devices were placed with full coverage of the pectoral muscle (26.2% and 39.6%, respectively) or dual plane (47.4% and 33.6%, respectively). Autologous flap cover, fat grafting or a MESH or Acellular Dermal Matrix (ADM) were not often used for both indications. See **Supplementary Table 1c** for all surgery characteristics of the records in which no indication was specified.

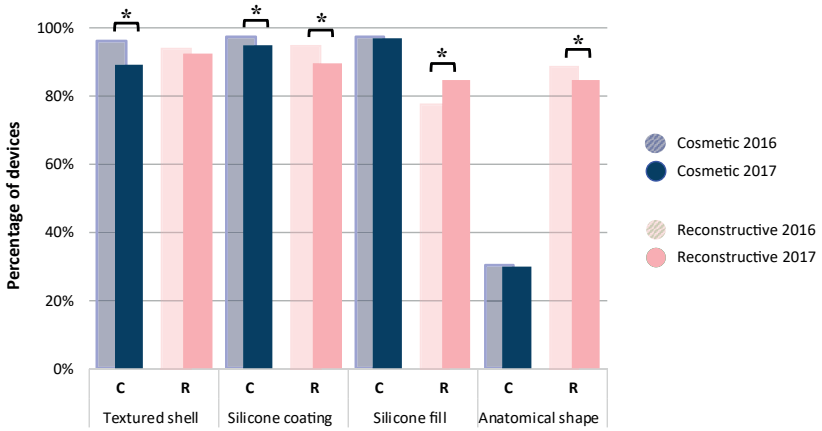

Figure 3. Device characteristics per inserted device (2015-2017) Textured vs Smooth shell, Silicone vs Polyurethane coating, Silicone vs Saline fill, Anatomical vs Round shape. NB. 2015 was not a complete registration year, and is therefore not included in this figure. Cosmetic (2016 n=8,995; 2017 n=11,253), Reconstructive (2016 n=1,546; 2017 n=2,175), <5% missing characteristics. * $p < 0.001$.

National variation in the use of infection control measures

A wide variation was observed between hospitals/clinics in the use of four selected perioperative infection control measures (all ranged 0-100%) (**Figure 4**). From 2016 to 2017, the proportion of procedures (per breast) in which surgeons changed their gloves before the insertion of an implant increased from 88% to 89% in reconstructive indications, and from 61% to 80% in cosmetic augmentations. Furthermore, an increase was observed regarding rinsing the breast implant with an antiseptic solution before insertion (from 70% to 78% (reconstructive), and from 78% to 85% (cosmetic)). Increased use of prophylactic intravenous antibiotics before the incision was noticed too; from 95% to 97% (reconstructive) and from 91% to 93% (cosmetic). The use of drains decreased in reconstructive procedures (80% to 78%) but increased in cosmetic augmentations (14% to 16%).

Table 2. Surgery characteristics, presented on breast level (2015-2017)

	Cosmetic		Reconstructive	
	n	%	n	%
Breasts[A]	26,036		4,505	
Incision site				
Inframammary	24,404	93.7	854	19.0
Mastectomy scar	194	0.7	2,391	53.1
Axillary	55	0.2	1	0.0
Areolar	109	0.4	370	8.2
Latissimus Dorsi	0	0.0	218	4.8
Other	1,072	4.1	344	7.6
Unknown	*202*	*0.8*	*327*	*7.3*
Plane				
Subglandular	3,584	13.8	173	3.8
Subfascial	1,823	7.0	34	0.8
Sub flap	13	0.0	360	8.0
Subcutaneous	20	0.1	52	1.2
Full pectoral muscle	6,830	26.2	1,783	39.6
Dual plane	12,343	47.4	1,512	33.6
Unknown	*1,423*	*5.5*	*591*	*13.1*
Mastopexy				
Yes	935	3.6	212	4.7
No	24,567	94.4	3,659	81.2
Unknown	*534*	*2.1*	*634*	*14.1*
Autologous flap cover				
Yes	95	0.4	511	11.4
No	25,386	97.5	3,362	74.6
Unknown	*555*	*2.1*	*632*	*14.0*
Fat grafting				
Yes	14	0.1	87	1.9
No	25,486	97.9	3,791	84.2
Unknown	*536*	*2.1*	*627*	*13.9*
Mesh/ADM use				
Yes	16	0.1	333	7.4
No	25487	97.9	3,776	83.8
Unknown	*533*	*2.0*	*396*	*8.8*

[A] *Breasts per unique surgical procedure, no unique breasts.*
ADM: Acellular Dermal Matrix.

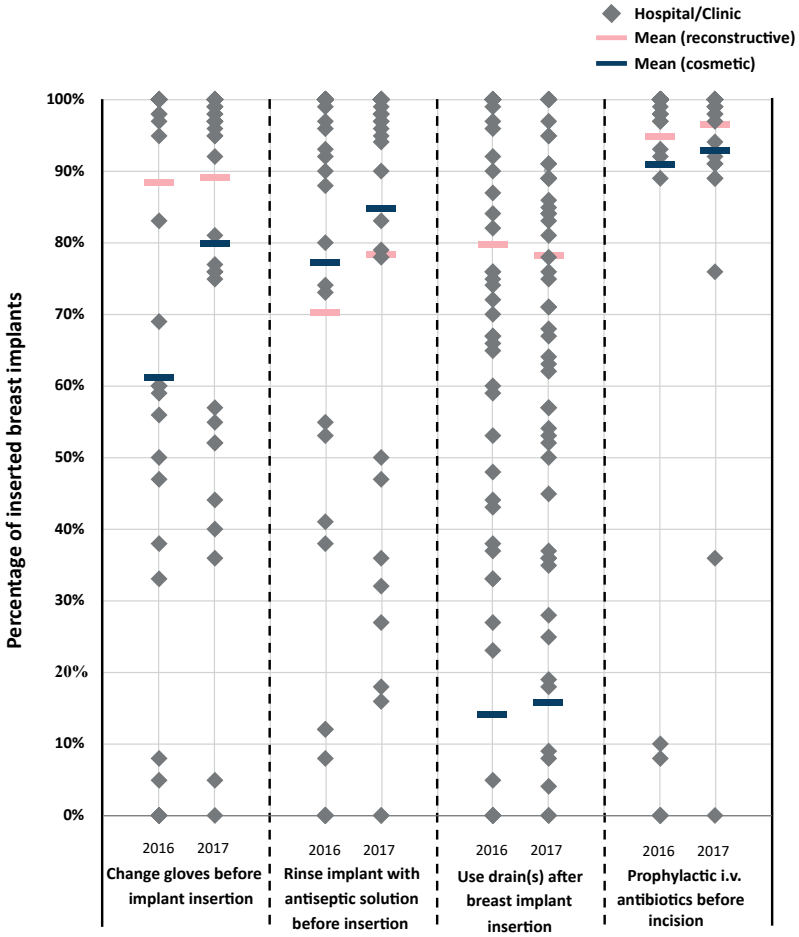

Figure 4. Nationwide variation for a selection of infection control measures (2016-2017), presented on breast level.
* 2015 was not a complete registration year, and is therefore not included in this figure.

DISCUSSION

This study provides an overview of the first outcomes and experiences of the Dutch Breast Implant Registry (DBIR), one of the first opt-out breast implant registries in the world. Since the national rollout in April 2015, information on 41,919 breast implants has been registered, including details of patients, devices, and procedures. The participation rate of hospitals (95%) and private clinics (78%) is high compared to other breast implant registries in the world with a maximum participation rate of 80% (or unknown capture rates).[15,16,17,18] For the first time, we were able to calculate the minimum breast implantation incidence rate in the Netherlands. In 2016 and 2017, at least one woman per 1,649 women, or one per 1,691, respectively, received one or more breast implant(s). However, it must be realized that this incidence rate is an underestimation, considering the current nationwide coverage of procedures.

Essentially, there were two groups of patients undergoing breast implant surgery with significant differences in characteristics: elective patients undergoing augmentation for cosmetic reasons who are generally young, healthy adults versus more complex patients requiring reconstructive surgery (mainly) after breast cancer treatment. Within our population, there was a predominance of textured silicone gel implants used for both indications. However, a significant increase in the use of smooth implants was observed, that appears to coincide with the critical issue of breast implant-associated Anaplastic Large Cell Lymphoma (BIA-ALCL), a rare cancer of the immune system believed to be causally associated with textured breast implants.[26,27] In recent research of Becherer and de Boer et al., data of the DBIR and the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) was combined, resulting in a dataset with both pathological, clinical and implant related information. This result demonstrated the potential of DBIR as an important tool for health risk assessments of implants.[28]

The DBIR aims to provide a pragmatic source of evidence of potential risks and benefits associated with clinical practice. For example, previous studies have suggested that the risk of capsular contracture is reduced by the use of an inframammary fold incision compared to periareolar incisions.[29] Or implants placed in a subpectoral position appeared to result less often in malposition of the implant or the development of capsular contracture.[30] However, these studies are often biased or unreliable due to

confounding by indication or loss to follow-up. Moreover, other factors such as the use of antiseptic precautions or the type of implants used may influence adverse outcomes as well. Therefore, only epidemiologically sound, longitudinal data such as from the DBIR, will be able to reveal optimal surgical treatment strategies and differences in implant performance by taking risk adjustment factors (casemix) into account.

The main purpose of the DBIR is to improve the quality of breast implant surgery in the Netherlands by providing benchmarked information on a set of process and outcome measures (quality indicators). Several other clinical audits have preceded, leading to substantial improvements in quality of care.[31,32,33] As an example of possible interesting process indicators, the national variation in the use of 4 infection control measures was presented (the use of antibiotics, antiseptic rinse of the implant, glove change prior to implant handling and the use of postoperative drains). A wide variation from 0 to 100% between hospitals and clinics in the use of these measures was seen. Understanding the nature of this variation and the effect of infection prevention on clinically relevant outcomes, such as postoperative surgical site infections, is paramount in decision-making about improvement efforts. Other examples of potential outcome indicators are: the percentage of explanations due to complications within an x number of days or long-term capsular contracture or implant rupture rates.

A balance is required between capturing all valuable information on the one hand and spending an acceptable amount of time needed for data entry on the other hand. To reduce the administrative burden an minimize the chance of typing errors, the GS-1 barcode system was implemented in the online data form of DBIR. With the help of this barcode, relevant implant characteristics, including the unique device identification (UDI) number, is automatically retrieved and registered. This will also help to decrease the amount of missing information on implant characteristics. Fortunately, an increasing amount of implant manufacturers are using a correct GS1 barcode in the Netherlands.

In general, completeness of the DBIR data has increased over the last three years.[23] It can be deduced from our results that missing data is not random; but namely patient records in certain hospitals. The DBIR online system provides already instant feedback on missing records using a 'list of errors'. Also, a data verification project to evaluate the validity of the data will be scheduled shortly. To further increase our nationwide

coverage, linking data from external databases could catalyse completeness of the DBIR data; e.g. external databases from the industry, the Dutch NABON Breast Cancer Audit (NBCA) and the Dutch Pathology Databanking and Biobanking (PALGA).

Internationally, the International Collaboration of Breast Registry Activities (ICOBRA) has defined an internationally agreed minimum core set of data points to be used by all breast device registries globally.[34] This dataset is integrated into the DBIR dataset. A future step is to combine breast implant registries globally to perform implant surveillance and evaluate clinical outcomes on an international level. Long-term data will eventually reveal the actual health effects of breast implants and breast implant surgery.

CONCLUSION

The opt-out Dutch Breast Implant Registry (DBIR) is one of the first up-and-running breast implant registries worldwide, which is the result of collaborative and conjoint efforts from clinicians, health care providers, and policymakers. First experiences with DBIR and its preliminary results show that DBIR has the potential to provide answers to clinically relevant questions and to provide quality assurance and outcome research for breast implant surgery.

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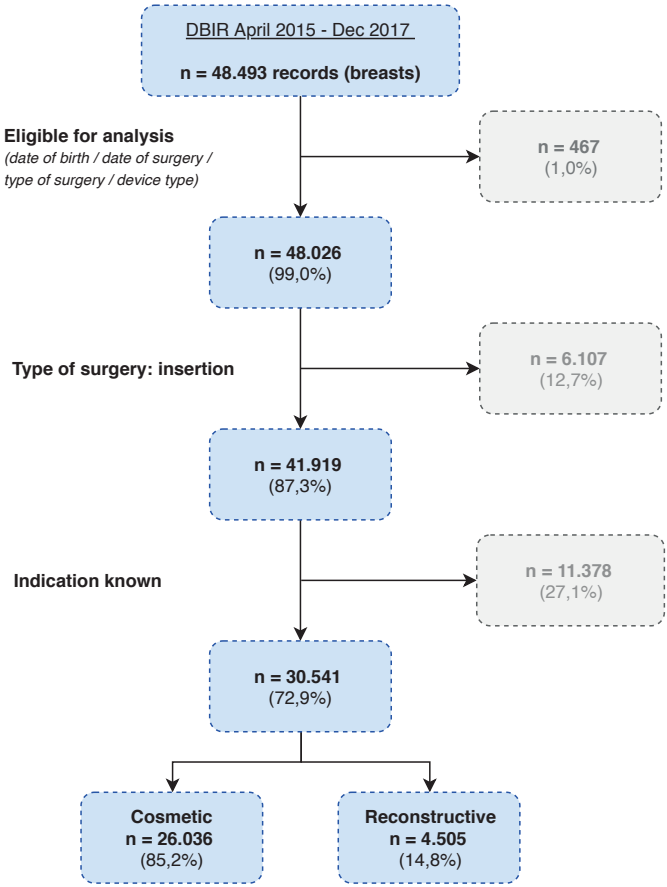

Supplementary Figure 1. Patient selection process.

Supplementary Table 1a. Patient characteristics per surgical procedure in which no indication was specified, presented on patient level (2015-2017)

	Indication not specified	
	n	%
Patients[A]	6,884	
Age		
<30	750	10.9
30-39	1,336	19.4
40-49	1,701	24.7
50-59	1,878	27.3
>60	1,219	17.7
ASA		
I	5,149	74.8
II	1,417	20.6
III-IV	130	1.9
Unknown	*188*	*2.7*
Smoking[B]		
Yes	2	4.8
No	1	2.4
Unknown	*39*	*92.9*
BMI[B] (kg/m^2)		
<18.5	0	0.0
18.5-25	6	14.3
25 - 30	0	0.0
>=30	0	0.0
Unknown	*36*	*85.7*

[A] *Patients per unique surgical procedure, no unique patients.*
[B] *Registered since September 2017. Percentages are calculated for a smaller population: n=42.*
ASA: American Society of Anesthesiologists. BMI: Body Mass Index.

Supplementary Table 1b. Device characteristics per inserted device for the records in which no indication was specified (2015-2017)

	Indication not specified	
	n	n
Inserted devices	11,378	
Texture		
Smooth	164	1.4
Textured	9.353	82.2
Unknown	*1,861*	16.4
Coating		
Silicone	9,517	83.6
Polyurethane	1,130	9.9
Unknown	*731*	6.4
Fill		
Silicone	10,080	88.8
Saline	155	1.4
Hydrogel	106	0.9
Unknown	*1,013*	8.9
Shape		
Round	4,989	43.8
Anatomical	5,529	48.6
Unknown	*860*	*7.6*
Volume[A] (median, in cc with IQR)	N/A	

[A] *Registered since September 2017. Percentages are calculated for a smaller population: n=0.*
IQR: Interquartile Range. N/A: not applicable.

Supplementary Table 1c. Surgery characteristics for the records in which no indication was specified, presented on breast level (2015-2017)

	Indication not specified	
	n	%
Breasts[A]	26,036	
Incision site		
Inframammary	6,228	54.7
Mastectomy scar	2,389	21.0
Axillary	10	0.1
Areolar	150	1.3
Latissimus Dorsi	206	1.8
Other	271	2.4
Unknown	*2,124*	*18.7*
Plane		
Subglandular	1,444	12.7
Subfascial	108	0.9
Sub flap	393	3.5
Subcutaneous	53	0.5
Full pectoral muscle	3,035	26.7
Dual plane	1,654	14.5
Unknown	*4,691*	*41.2*
Mastopexy		
Yes	473	4.2
No	8,534	75.0
Unknown	*2,371*	*20.8*
Autologous flap cover		
Yes	252	2.2
No	8,780	77.2
Unknown	*2,346*	*20.6*
Fat grafting		
Yes	157	1.4
No	8,892	78.2
Unknown	*2,329*	*20.5*
Mesh/ADM use		
Yes	62	0.5
No	9,102	80.0
Unknown	*2,214*	*19.5*

[A] *Breasts per unique surgical procedure, no unique breasts.*
ADM: Acellular Dermal Matrix.

CHAPTER 8

From the ICOBRA initiative: A globally agreed minimum data set for breast implant surgery.

Pauline E.R. Spronk
Husna Begum
Swarna Vishwanath
Andy G. Crosbie
Arul Earnest
Elisabeth Elder
David B. Lumenta[6]
Danica Marinac-Dabic
Colin C.M. Moore
Marc A.M. Mureau
Graeme Perks
Andrea L. Pusic
Birgit Stark
Uwe von Fritschen
Howard Klein
Rodney D. Cooter
Hinne A. Rakhorst*
Ingrid Hopper*
*both authors equally contributed to this article

Submitted

ABSTRACT

Objective: To identify an internationally agreed minimum set of data points and their definitions to be used by all breast device registries globally.

Background: The Poly Implant Prothese (PIP) incident and breast implant associated Anaplastic Large Cell Lymphoma (ALCL) have raised awareness of the need for developing uniform device registries for breast implants. A uniform set of data points and data definitions is key to monitoring the performance of breast implants and collecting comparable information about procedures and outcomes of breast device surgery on an international level.

Methods: The International Collaboration of Breast Registry Activities (ICOBRA) convened an international multidisciplinary working group of surgeons, consumer representatives, specialist nurses, registry experts and medical device regulators. Data points collected by all currently operating breast implant registries were reviewed. A list of items to be used in the consensus process was defined. A modified Delphi approach was used, with surveys requiring the panellists to rate the importance of each data point to be included in the global minimum data set on a six point Likert scale.

Results: Data points from six different national breast implant registries were compared. Data points were divided into nine categories: clinical, implant related, and patient-reported findings, operation details (including antibiotics) and implanting technique details, patient characteristics, unique device identifiers (UDIs), unique patient identifier (UPI), and clinical demographics. A total of 52 data points which were collected by over 33% of currently national running registries were identified for the consensus (Delphi) process. After five rounds, 34 data points formed the global dataset and 17 data points were classified as the optional dataset for registries to collect globally. Data definitions were subsequently agreed upon.

Conclusion: We defined an internationally agreed minimum dataset to be used in breast device registries. This collaborative approach to share data will allow datasets to be combined and will provide a more effective global early warning system of implant-related problems.

INTRODUCTION

Breast implants are increasingly popular worldwide for breast reconstruction as well as breast augmentation.[1] In the Netherlands, the estimated prevalence of breast implants is 3,3% of the adult female population.[2] The safety and health effects of breast implants have been debated since their introduction over 50 years ago.[3,4,5] It has been observed that the longer breast implants remain in situ, the greater the likelihood of complications or adverse events.[6,7] Recently, Anaplastic Large Cell Lymphoma which, although a rare disease, has been shown to be associated to breast implants (BIA-ALCL).[8,2] In order to determine the health effects of breast implants and to determine implant performance, reliable long-term systematically collected data are needed.

Registry data provide a pragmatic source of evidence to address such issues of public health and safety. However, insufficient capture rates or dependence on implant producers made previous national and international patient registries unreliable.[9,10] Stakeholders including the UK Medicines and Healthcare Products Regulatory Agency, the Food and Drug Administration and the Australian Therapeutic Goods Administration have highlighted the importance of well-organized clinical registries that can provide early warning of underperforming devices such as breast devices, independent from the industry.[11,12,13,14] They are also an effective tool for recall procedures in the case of an adverse event. An example of this followed the recent withdrawal of Silimed implants from the market. Within a few hours the number of Silimed implants in the Dutch Breast Implant Registry could be determined, thereby providing clarity for patients, institutions as well as governmental organizations, and reassuring the vast majority who were unaffected.[15]

In 2012, the International Collaboration of Breast Registry Activities (ICOBRA) was established to improve breast device registries by sharing datasets and connecting organizations.[16] The members of ICOBRA include national plastic surgery societies or multidisciplinary breast implant registries of several countries, including Australia, Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, the United Kingdom, and the United States.

A number of countries have independent registries that are using largely similar datasets. Harmonization of these data points and data definitions is key to be able to compare and pool data from registries. Pooling is crucial to amplify the data and reduce the time needed to identify implants performing well and those associated with higher rates of adverse events, such as BIA-ALCL or capsular contraction. Therefore, we aimed to identify and define an internationally agreed minimum set of data points to be used by all breast device registries globally.

METHODS

Selection of data points

Registries for breast implants and tissue expanders were included in our study. Methods of enrolment, estimated total market of implants/100.000 adult female inhabitants, number of registered implants and capture rates were collected but were not part of this Delphi process.

Through ICOBRA, the six eligible countries with functioning breast device registries were invited to share their data sets, including the Australian Breast Device Registry (ABDR),[14] the Dutch Breast Implant Registry (DBIR),[15] the Bröstimplantatregistret of Sweden (BRIMP),[17] the Austrian Breast Implant Register (ABIR),[18] the Breast and Cosmetic Implant Registry of the United Kingdom (BCIR),[19] and the US National Breast Implant Registry (NBIR). In addition, all invitees provided their data definitions.

Data points were divided into nine categories: clinical, implant related, and patient-reported findings, operation (including antibiotics) and implanting technique details, patient characteristics, unique device identifiers (UDIs), unique patient identifier (UPI), and clinical demographics. Data points collected identically by the various registries were divided into three groups based on the percentage of registries that collect a specific data point. Groups were >66% , 33-66% and <33%.

On the 7th and 8th of April 2017, ICOBRA organized an in-person meeting at Monash University in Prato, Italy and 26 participants from eleven countries attended, representing clinicians, regulators, registry science experts, data managers and administrators; Australia (8), Austria (1), Germany (1), the Netherlands (3), New Zealand (1), Russia (1), Saudi (2), South Korea (2), Spain (1), Sweden (2), the United Kingdom (4), the United States (1). The theme of the meeting was "Consensus planning". The categorized data points were shared and the Delphi method was introduced. It was agreed that the number of data points should be reduced to a minimum and that a minimum overlap of 33% was required for a data point to become a candidate for the global minimum data set using a Delphi process.

Modified Delphi Process to obtain consensus on the core Tier 1 data points

The consensus process followed a modified Delphi approach,[20] which took place between July and November 2017. This process consisted of four rounds of online surveys using Qualtrics,[21] with each round of survey followed by a video teleconference. A pilot data collection form which included the global data set was designed and circulated among all the clinicians in the Delphi panel. All clinicians were encouraged to test the form by filling it out after their procedures. Clinicians provided feedback after trialling the form during 5-10 procedures, and suggested additional data points, so one further round was organised in November 2018 which included additional data points identified during testing of the dataset.

Expert panel members were selected to represent a wide range of stakeholders. The panel was international and multi-disciplinary, with representatives from each of the functioning breast implant registries (Australia, Austria, the Netherlands, Sweden, UK, US), other specialists in breast device surgery (breast surgeons and cosmetic surgeons and a breast-care nurse), two consumer representatives to confirm that the dataset would identify outcomes that were important for them, national regulators to help maximize the utility of the dataset and ensure the work aligned with other international registries, biostatisticians to ensure the statistical rigor of the methodology, and was chaired by a registry science expert.

The survey required the panelists to rate the importance of each data point on a six point Likert scale to be included in the global minimum data set. Data points were considered when they met the following criteria: (i) median score of 5 or 6, (ii) more than 70% of the panel scoring a 5 or 6, and (iii) no disagreement according to the RAND criteria.[22]

After each round, results from the survey were shared with the panel members prior to the next teleconference. As feedback and preparation for teleconferences, panel members received their own individual score and the overall group score (median) for each data point. If consensus was not reached to include a data point in the global data set, it became part of the optional set for each country to use at liberty.

Data definitions for Tier-1 and Tier-2 data points

Data definitions for all the data points included in the modified Delphi process were then finalized. The ABDR data definitions, which were obtained from established standard sources where they existed, or adapted from the medical literature, were used as the starting point. If no definitions were available from the ABDR data definitions, the definitions for those data points were developed by the ICOBRA team. The Delphi panel voted on these definitions as being 'acceptable' or 'requiring amendment'. This process consisted of 2 rounds of online surveys with each round of survey followed by a video teleconference, until the majority of panel members agreed to all definitions, with the same process used for further additions from the November 2018 round. Ethics approval was obtained from Monash University Human Research Ethics Committee. All panelists consented to participating in the study.

RESULTS

General characteristics of the six included national, functioning breast device registries are listed in **Table 1**. The results of the categorization of data points are listed in **Table 2**. The highest number of items were collected on implant related findings, operation details, and Unique Device Identifiers (UDI). Fewer similarities in data points were detected on patient characteristics and patient-reported outcomes.

Table 1. General characteristics of the current running breast device registries

Breast Device Registry	Since	Method of enrollment	Implants per 1,000 inhabitants[a] per year	Registrations per year	Capture rate
ABDR	2015	Opt-out	0.4 – 0.8	10,000-15,000	*not known yet*
DBIR	2015	Opt-out	1.2 – 2.9	15,000 – 25,000	80%-90%
BRIMP	2014	Opt-out	< 1.0	< 5,000	61% -70%
ABIR	2004	Opt-in	< 1.1	< 5,000	*not known yet*
BCIR	2016	Opt-in	0.8 – 1.5	25,000 – 50,000	*not known yet*
NBIR	2018	Opt-out	1.3 – 1.7	175,000 – 225,000	*not known yet*

ABDR: Australian Breast Device Registry, DBIR: Dutch Breast Implant Registry, BRIMP: Bröstimplantatregistret of Sweden,
ABIR: Austrian Breast Implant Register, BCIR: Breast and Cosmetic Implant Registry of the UK,
NBIR: US National Breast Implant Registry

Table 2. Overlap in data points in the six current running nationwide breast device registries Bold = 100% overlap.

	> 66% overlap	33% - 66% overlap	< 33% overlap
CLINICAL FINDINGS	**Infection** Seroma / hematoma (Newly diagnosed) breast cancer ALCL	Reason for revision; *(complication, asymptomatic, patient preference)* Skin necrosis Skin Scarring problems	Removing PIP implant Need for biopsy/suspect tumor Flap problem/loss Wound problems Bleeding ASIA syndrome
IMPLANT RELATED FINDINGS	**Capsular contracture (baker)** **Device rupture** **Device deflation** **Device malposition/rotation** Silicone extravasation		Axillary lymph node involvement Wrinkling/rippling
PATIENT-REPORTED FINDINGS	Asymmetry Patient dissatisfied with volume/ shape	Breast pain Worried for implant/desire to remove Due to recommendation LMV	Because of pregnancy Swollen breast Hard breast Ptosis
OPERATION DETAILS	Systemic/preoperative antibiotics **Laterality/side** Indication for surgery **Type of intervention (primary, revision, explant only)** Implant position/plane **Incision site** Capsulectomy Fat grafting	Postoperative Antibiotics Timing reconstruction (immediate/delayed) Occlusive nipple shields Nipple absent Flap cover	Neo-pocket formation Fat volume AB selection Steroids selection
IMPLANTING TECHNIQUE DETAILS	**Drain use** Antiseptic rinse of the pocket	Nipple Guards Glove change before insertion Sleeve/funnel (Keller funnel)	Type of rinse solution
PATIENT CHARACTERISTICS	Previous radiotherapy Date of birth Gender	ASA classification before Operation Smoking Height Weight Diabetes	History of medical issues Breast surgery prior to present operation Patients experience before surgery Post Radiotherapy planned
UDI	UDI (unique device identifier) **Device manufacturer** **Device serial no.** **Device catalogue reference no.** Device LOT no. Texture/ shell Fill Mesh or ADM used	Device distributor Shape Volume of implant Volume of TE Date of insertion of removed implants Device details of explanted device Volume of implant removed	Coating Max. volume of TE Markers/medical record of explant available Removing implant inserted other location UDI/details of MESH/ ADM

ALCL: *Anaplastic Large Cell Lymphoma*, ASIA: Auto Immune/Inflammatory *Syndrome* induced by Adjuvants, TE: Tissue Expander,
UDI: Unique Device Identification, ADM: *Acellular Dermal Matrix*, ASA: American Society of Anaesthesiologists physical status classification, AB: Antibiotics, LMV: Competent Authority *Sweden* (LäkeMedelsVertet*)*

Delphi analysis on data points

The Delphi process included five rounds of surveys and videoconferences. The videoconferences focused on the importance of collecting the data point based on its usefulness and the feasibility of collecting. The results and the participation from the panel at each round is shown in **Figure 1**. All data points that (i) were modified or (ii) did not achieve consensus in one round were included in the next round. The five rounds resulted in 34 data points (78 including sub-points) that were voted in the global data set by the panel (see **Table 3**). The optional data set consisted of 17 data points which are listed in **Table 4**.

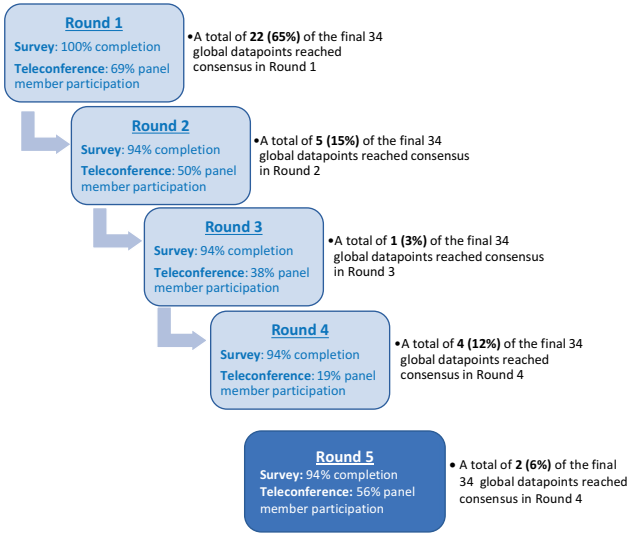

Figure 1. Modified Delphi process flow diagram.

Webconferences lead to renaming of datapoints

Discussions in webinars resulted in rewording of some data points (includes data points already in the global data set), introduction of some new data points to capture more meaningful information from multiple data points, and the inclusion of additional information. One data point (device malposition/rotation) and four sub-points (Infection leading to explantation, seroma, hematoma, risk reducing mastectomy) that had achieved consensus in round 1 had the wording clarified in the second round. Another data point 'Antiseptic rinse of the pocket' was changed during round 3 into 'Rinse of

Table 3. List of the global data points

Domain	No.	Data point	Voted in the global dataset during round
CLINICAL FINDINGS	1.	Reason for revision/explantation	Round 1
		a) *Patient preference*	Round 2
		b) *Asymptomatic*	Round 1
		c) *Complication*	Round 1
	2.	Infection leading to explantation	Round 1&2*
	3.	Seroma	Round 1&2*
	4.	Hematoma	Round 1&2*
	5.	Capsular contracture	Round 1
	6.	BIA-ALCL	Round 1
		a) *Suspected*	Round 5
		b) *Confirmed*	Round 5
IMPLANT RELATED FINDINGS	7.	Device rupture	Round 1
	8.	Device malposition/rotation	Round 1&2*
PATIENT REPORTED FINDINGS	9.	Breast pain	Round 4
OPERATION DETAILS	10.	Postoperative antibiotics	Round 1
	11.	Preoperative antibiotics	Round 2
	12.	Laterality	Round 1
	13.	Indication for surgery	Round 1
		a) *Cosmetic augmentation*	Round 1
		b) *Reconstruction post-risk reducing mastectomy*	Round 1&2*
		c) *Reconstruction (benign)*	Round 1
		d) *Reconstruction post-mastectomy for cancer*	Round 1
	14.	Type of intervention	Round 1
		a) *Primary*	Round 1
		b) *Secondary*	Round 1
		c) *Revision*	Round 1
		d) *Explant only*	Round 1
	15.	Timing of reconstruction	Round 5
		a) *Immediate*	Round 5
		b) *Delayed*	Round 5

Table 3. List of the global data points (continued)

Domain	No.	Data point	Voted in the global dataset during round
OPERATION DETAILS	16.	Implant position/plane	Round 1
		a) Sub glandular	Round 1
		b) Sub pectoral	Round 1
		c) Sub fascial	Round 1
		d) Sub flap	Round 1
		e) Sub cutaneous	Round 1
		f) Dual plan	Round 1
		g) Others (please specify)	Round 1
	17.	Incision site	Round 2
		a) Inframammary	Round 2
		b) Periareolar	Round 2
		c) Axillary	Round 2
		d) Mastectomy scar	Round 2
		e) Others (please specify)	Round 3
	18.	Nipple sparing	Round 1
	19.	Flap cover	Round 1
	20.	Fat grafting	Round 1
	21.	Concurrent mastopexy	Round 5
	22.	Capsulectomy	Round 1&4*
		a) Partial capsulectomy	Round 2
		b) Full capsulectomy	Round 3
IMPLANTING TECHNIQUE	23.	Rinse of the pocket	Round 3
		a) Antibiotics	Round 3
		b) Antiseptics	Round 3
		c) Others (please specify)	Round 3
	24.	Drain use	Round 2
	25.	Glove change before insertion	Round 2
PATIENT CHARACTERISTICS	26.	Previous radiotherapy	Round 1
	27.	Date of birth/Age of patient	Round 4
	28.	Height	Round 4
	29.	Weight	Round 4

Table 3. List of the global data points (continued)

Domain	No.	Data point	Voted in the global dataset during round
	30.	Device details[#]	Round 1
		a) Device manufacturer	Round 1
		b) Device serial number	Round 1
		c) Catalogue reference number	Round 1
		d) Device lot number	Round 1
		e) Texture	Round 1
		f) Fill	Round 1
		g) Shape	Round 1
UDI (incl. MESH/ADM)		*h) Volume of implant*	Round 1
	31.	ADM/Mesh used	Round 1
		a) Device details of the ADM/Mesh used	Round 1
	32.	Date of insertion of removed implants	Round 1
	33.	Device details of explanted device	Round 1
		a) Texture	Round 1
		b) Fill	Round 1
		c) Shape	Round 1
	34.	Marker/Medical record of explanted device if known	Round 2

BIA-ALCL: Breast Implant Associated Anaplastic Large Cell Lymphoma, **ADM:** Acellular Dermal Matrix, **UDI:** Unique Device Identification
Please note:
* Data point voted on in earlier round and wording confirmed in later rounds
[#] This data point will be changed to UDI when it has been implemented

the pocket with options to include antiseptics, antibiotics and other' (see **table 5** for details on these changes). The global data points that required multiple rounds of discussion were either in the 'Patient characteristics' category or the 'Patient reported findings' category. With date of birth/age of patient, the discussion showed that different formats are used and that the European Union does not allow the international transfer of such identifiable information, so age of patient will be used instead. The panel had concerns about the collection of height and weight relating to the reliability of data obtained.[23] Breast pain, which is a patient reported finding, was seen to be subjective and difficult to define. Another data point, 'Capsulectomy', which did not have a consistent definition, also required four rounds of discussion before it was voted in the global dataset.

Table 4. List of the optional data points

Domain	No.	Data point	% of registries collecting
CLINICAL FINDINGS	1.	(Newly diagnosed) Breast cancer	>66%
	2.	Skin scarring problem	33-66%
	3.	Flap problem	33-66%
	4.	Double capsule (Panellist suggestion)	33-66%
	5.	Autoimmune Syndrome Induced by Adjuvants (ASIA)	NA
IMPLANT RELATED FINDINGS	6.	Silicone extravasation	>66%
PATIENT REPORTED FINDINGS	7.	Asymmetry	33-66%
	8.	Changing implant size	33-66%
	9.	Desire to remove/change implant	33-66%
ANTIBIOTICS/ OPERATIONS DETAILS	10.	Neopocket formation	33-66%
IMPLANTING TECHNIQUE	11.	Occlusive nipple shields	33-66%
	12.	Nipple absent	33-66%
PATIENT CHARACTERISTICS	13.	ASA Classification before operation	33-66%
	14.	Smoking	33-66%
	15.	Gender	33-66%
UDI (incl. MESH/ADM)	16.	Volume of tissue expander	33-66%
	17.	Volume of removed implant	33-66%

ADM: *Acellular Dermal Matrix*, **UDI:** Unique Device Identification, **ASA:** American Society of Anaesthesiologists physical status classification

Table 5. Changes made to data points

Data points	Modification
Infection	Wording changed to 'Infection leading to explantation'.
Seroma/Hematoma	Split into two separate data points, 'Seroma' and 'Hematoma'.
ALCL	Changed to 'BIA-ALCL' (not included in the round 2 survey as the modification was minor)
Device malposition	Changed to 'Device malposition/rotation'
Capsulectomy	Included two sub-points, 'Full capsulectomy' and 'partial capsulectomy'
Prophylactic mastectomy	Changed to 'Risk reducing mastectomy'
Changing implant size and Desire to remove/change implant	A data point 'Patient preference' will be sufficient to capture meaningful information relating to these two data points
Antiseptic rinse of the pocket	Changed to 'Rinse of the pocket with options to include antiseptics, antibiotics and other'

BIA-ALCL: Breast Implant Associated Anaplastic Large Cell Lymphoma

The round 3 teleconference slides compared the results for each of the data points under consideration across the three rounds. This was done to evaluate whether further consensus could be achieved for the data points. It was decided during the teleconference that further consensus on the remaining data points would be unlikely after the next round, and therefore any remaining data points would be included in the optional dataset.

An additional round included data points that were identified during pilot testing of the dataset by the panel. The additions made were 'timing of surgery' and 'concurrent mastopexy' which were both voted in as global data points in the survey and 'Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA)' was included as an optional data point.

Delphi analyses on data definitions

The first round of survey included 72 data points with definitions and the response rate was 93%. The definitions for 31 data points received no comments from the panellists and were voted as 'acceptable'. The definitions for the remaining 41 data points were discussed in the teleconference which had participation from 60% panellists and resulted in definition options for each of the 41 data points. The second round of survey included all the definition options for the data points and the most popular definition was chosen as the preferred definition. The final round also included definitions for the additional data points. The panel considered a number of published definitions of ASIA[24,25,26], but were unable to reach consensus, largely as the causative role of silicone in ASIA remains unproven, therefore this data point does not currently have a working definition. See **table 6** for the list of definitions for all other data points.

DISCUSSION

We have outlined the process undertaken by ICOBRA, an international multidisciplinary group with expertise in breast device registries including consumer representatives, national regulators and biostatisticians, to develop a global minimum dataset for breast implant registries, to enhance patient safety and quality of care. After the Delphi process, consensus was reached on a list of 34 data points (78 with sub-points) to

Table 6. List of finalised definitions for all data points

		The global dataset
No.	**Data point**	**Definition**
1.	Reason for revision/ explantation	The main reason for undertaking revision of a breast implant
a	Patient preference	The choice of the patient
b	Asymptomatic	Procedure performed due to a device recall, or a planned revision, or asymmetry, or revision due to a complication on the other breast
c	Complication	Any deviation from the normal post-operative course
2.	Infection leading to explantation	An infection associated with a breast implant in place, which leads to its explantation. Usually involves redness, localised pain or tenderness, abscess or persistent serous liquid formation around the implant even with distinct clinical signs it might be culture-negative
3.	Seroma	An abnormal accumulation of serum around the device
4.	Hematoma	A collection of blood outside the blood vessels which can be localised in an organ, space, or tissue
5.	Capsular contracture	The shrinkage of the foreign body encapsulation scar tissue that forms around artificial implants imbedded in body tissues
6.	BIA-ALCL	A current or previous diagnosis (pathology based) of breast implant associated anaplastic large cell lymphoma (BIA-ALCL), where BIA-ALCL is a CD30+, ALK-, T-cell derived lymphoma within the non-Hodgkin lymphoma group. This data point to include (a) Suspected and (b) Confirmed.
7.	Device rupture	Loss of implant shell integrity
8.	Device malposition/ rotation	Any instance in which the implant is outside its intended position
9.	Breast pain	As noted by the patient
10.	Preoperative antibiotics	Use of antibiotics provided IV, Orally, or IM before incision
11.	Postoperative antibiotics	Use of antibiotics provided IV, Orally, or IM at any time after 3 hours post-surgery
12.	Laterality	The left or the right breast
13.	Indication for surgery	The reason for surgery
a	Cosmetic augmentation	A cosmetic procedure for enlarging breasts
b	Reconstruction post risk reducing mastectomy	Surgery to remove one or both breasts to reduce the risk of developing breast cancer
c	Reconstruction – benign	Surgery to restore or create shape and symmetry in patients with loss or absence of all or some breast tissue due to benign breast conditions, congenital deformity, tuberous breasts, or gender reassignment surgery
d	Reconstruction post mastectomy for cancer	Surgical procedures performed to recreate a breast after one or both breasts are removed as a treatment for breast cancer
14.	Type of intervention	Type of intervention to include sub-points primary, secondary, revision, or explant only.
a	Primary	An initial insertion of a new device, i.e. an implant or expander
b	Secondary	Removal of an expander and insertion of an implant
c	Revision	Revision of an in situ device, i.e. an implant or an expander revision
d	Explant only	Removal of an implant

Table 6. List of finalised definitions for all data points (continued)

15.a	Timing of reconstruction Immediate	Breast reconstruction carried out at the time of mastectomy
15.b	Timing of reconstruction Delayed	Breast reconstruction carried out at a later time than the mastectomy
16.	Implant position/plane	The surgical plane in which an implant is inserted. This data point to include sub-points (i) Sub glandular, (ii) Sub pectoral, (iii) Sub fascial, (iv) Sub flap, (v) Sub cutaneous, (vi) Dual plane, and (vii) Others (please specify)
17.	Incision site	The site where the incision is placed
a	Infra-mammary	An incision in, or beneath, the infra-mammary fold
b	Periareolar	An incision around the areola
c	Axillary	An incision in the axilla
d	Mastectomy scar	An incision at the site of an existing mastectomy incision
e	Others (please specify)	Any other incision site
18.	Nipple sparing	Removal of the breast tissue with preservation of the breast skin envelope and the nipple and areola complex
19.	Flap cover	Any type of flap used for breast reconstruction (concurrent or previous) that covers an implantable breast device or adds volume to the breast mound
20.	Fat grafting	Transfer of aspirated fat to the breast region
21.	Concurrent mastopexy	Indicating whether the procedure involves a mastopexy (breast lift)
22.	Capsulectomy	Removal of the encapsulating scar tissue surrounding the breast implant
a	Partial capsulectomy	Surgical release and/or partial removal of the capsule
b	Full capsulectomy	Complete removal of the capsule including thoracic part of the capsule
23.	Rinse of the pocket	Rinse of the surgically created pocket before implant insertion
a	Antiseptics	Intraoperative wash of the surgical pocket with an antiseptic solution
b	Antibiotics	Intraoperative wash of the surgical pocket with an antibiotic solution
c	Other (please specify)	Any other type of rinse used
24.	Drain use	Intra-operative insertion of drains
25.	Glove change before insertion	Change of gloves immediately prior to insertion of the implant
26.	Previous radiotherapy	Radiotherapy to the breast or chest wall at any time prior to the current device operation
27.	Date of birth OR Age of patient	As identified in the medical record
28.	Height	A person's self-reported height, measured in centimetres (or inches)
29.	Weight	The weight (body mass) of a person measured in kilograms (or lbs)
30.	Device details / Unique Device Identifier (UDI)	Details of the implanted device / Unique Device Identifier
a	Device manufacturer	Name of the manufacturer of the implanted device
b	Device serial number	Serial number of the implanted device
c	Catalogue reference number	Catalogue reference number of the implanted device
d	Device lot number	Lot number of the implanted device

Table 6. List of finalised definitions for all data points (continued)

e	Texture	The surface texture of the device being inserted or explanted
f	Fill	The material used to fill the breast implant: saline solution, silicone gel, or other
g	Shape	The shape of the device being inserted into or explanted from the breast; where the shape of the device is either **Round:** implant is shaped like a flattened sphere or **Shaped:** a contoured shape that re-creates the more teardrop outline of a mature breast
h	Volume of implant	As determined by the manufacturer or measured intraoperatively by weight, or displacement, or fill volume
31.	ADM / Mesh used	The use of either an 'absorbable or non-absorbable synthetic mesh' or 'acellular dermal matrix' which are medical devices used in breast implant surgery where the mesh or matrix provide a soft tissue scaffold
a	Device details of the ADM / Mesh used	Details of the ADM / Mesh
32.	Date of insertion of removed implants	Date the explanted implants were inserted (known or estimated)
33.	Device details of explanted device (UDI)	Any available details of the implant at the time of explantation
34.	Marker / medical record of explanted device (if known)	The explanted device's specific markings indicating type, manufacturer, serial number or lot number
		The optional dataset
No.	**Data point**	**Definition**
1.	Newly diagnosed breast cancer	*Recommend not using this data point; hence no definition*
2.	Skin scarring problem	An abnormal or suboptimal cutaneous or dermal scarring. Includes keloid formation, hypertrophic scarring, poor scar contour or orientation causing distortion or compromise of the reconstructive or aesthetic result. Does not include capsular contracture
3.	Flap problem	When a flap is used as part of a reconstruction, includes but not limited to one or all of the following problems: Total flap loss, partial flap loss, vessel thrombosis, flap hematoma, flap infection, sub-flap seroma, flap fat necrosis, size mismatch resulting in incomplete coverage. Does NOT include donor site complications
4.	Double capsule	A second thin tissue layer encasing the usually textured implant subsequently leading to permanent separation from the outer capsule
5.	Autoimmune Syndrome Induced by Adjuvants (ASIA)	No accepted definition as yet – kindly refer to Tervaert, J. W. C. (2018). Autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome): A new flame. *Autoimmunity reviews.*
6.	Silicone extravasation	Extrusion of silicone beyond the limits of the capsule
7.	Asymmetry	As determined by the patient and identifiable by the surgeon
8.	Changing implant size	Patient preference to change the size of implant
9.	Desire to remove / change implant	As determined by the patient

Table 6. List of finalised definitions for all data points (continued)

10.	Neopocket formation	Formation of a new pocket
11.	Occlusive nipple shields	The use of adhesive film dressing covering the nipple-areola complex to prevent perioperative expression of bacteria from nipple ducts contaminating the operative field
12.	Nipple absent	Absence of the nipple at the time of device insertion
13.	ASA classification	A system used by anaesthesiologists' to stratify severity of patients' underlying disease and potential for suffering complications from general anaesthesia
14.	Smoking	As identified by the patient
15.	Gender	Self-identified gender (options to include male, female, other)
16.	Volume of tissue expander	Intraoperative fill volume, as determined by the surgeon at the time of the procedure
17.	Volume of removed implant	As determined (or estimated) by the surgeon at the time of the procedure

be included in the global dataset. Data points for which consensus was not achieved and were not voted into the global dataset, became the optional dataset. Consensus definitions for all data points were achieved, using the ABDR data definitions as the starting point, with the exception of ASIA, for which no definition is currently provided. It is expected that the global dataset will be adopted by currently operating breast device registries within two years and by all new breast implant registries in the ICOBRA network.

The use of the global set and the optional set ensures that countries can maintain their independence in selecting data points that suit them. The global dataset can be described as a "data spine", and will be reviewed every three years in light of new evidence. The optional dataset can be described as a "data rib" and encompasses all other data points collected by any country, which may be used to reflect regional preferences or to further investigate a clinical issue, and can be expanded upon.

Consensus for the majority of data points was easily achieved in the first round, while some others required multiple rounds of discussion before consensus for inclusion in the global dataset was achieved. Although not everyone could be present at the video teleconferences, all participants were able to add their remarks beforehand and all contributions were discussed. Approximately 56% of the global data points were al-

ready being collected by >66% of registries, meaning that for the currently functioning registries, incorporation of these data points will be straightforward.

The ICOBRA global dataset is designed as a minimum dataset. The data collection itself should facilitate the documentation for the clinical personnel at the frontline of medical/operative documentation, instead of posing another burden. The dataset is epidemiologically sound, meaning that clinical judgement is not required to collect the data, such as might be required for example with the Baker grading of capsular contracture. Ideally data collection is built into a routine workflow in an institution's electronic patient record system. Incorporating the ICOBRA global dataset into the electronic medical record also eliminates double/redundant documentation and facilitates bulk-uploading to the registry. Combining it with administrative databases improves the quality of the data overall, and diminishes a cherry-picking type of record keeping.

The value of the ICOBRA global dataset is clear. Pooling data from breast implant registries will allow active surveillance and comparative outcomes evaluation, providing denominator data for adverse events to identify under-performing devices earlier. This will safeguard the health of recipients of breast implants by preventing implantation of defective devices, reducing risks and costs associated with early revision, and providing manufacturers with greater ability to deliver safe products to the market.[27] Further, collecting comparable information about procedures and outcomes feeds into clinical auditing and facilitates benchmarking on an international level, which can drive quality improvement at participating institutions, again reducing complications and costs.[28] In the absence of high-quality, randomized controlled trials to assess the effect of various intraoperative techniques, such as the use of antiseptic rinse, glove change prior to implant handling, and the use of nipple guards and postoperative drains, registry data provide a pragmatic alternative source of evidence (clinical practice based evidence).[29,30] Best surgical techniques can be identified in a real-world environment and new implant technologies can be reliably evaluated. Importantly, the use of large pooled international datasets is the only way we can address the critical issue of BIA-ALCL[2], a rare cancer of the immune system believed to be causally associated with breast implants. Moreover, this information will be of great value empowering patients to be effective advocates for their health, so that they can make informed decisions.

There are significant complexities and practical hurdles when transferring large datasets internationally.[31] Care must be taken to protect the privacy of patients as well as the security of data when bringing together the ICOBRA global dataset. Regulations vary according to region with the use of de-identified data. European Union regulations do not allow the export of identifying information including date of birth, with the threat of heavy fines.[32] It remains to be determined whether de-identified data (with the risk of re-identification) or aggregate analyses will be combined.

Now that a global minimum dataset for breast implant surgery has been established, further international initiatives should be undertaken. The ICOBRA network collaborates on research projects and post-market surveillance of breast implants, similar to the work of the International Consortium of Orthopedic Registries,[33] and aims to establish a global patient-reported outcome measure (PROM) to provide early warning of under-performing devices using patient reports of breast symptoms. In addition, there is potential for breast device registries to support low-cost randomized controlled trials.[34] Collaboration with industry can lead to benefits such as a reduced registration load by prefilling device characteristics using a Unique Device Identifier (UDI). Uniform barcode processing with accepted international standards will increase patient safety and further reduce the burden of data entry. Further, the usage of stock and supply information functions as valuable validation system of the registry database to calculate the capture rate on a nationwide level.

CONCLUSIONS

We have defined a global minimum dataset to be collected for breast implant surgery in routine clinical practice. Datasets will be combined in the future with the aim of early detection of under-performing breast devices and to guide treatment protocols. This will provide better information about outcomes of breast implant surgery and overcome national borders, thereby strengthening international collaborations.

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CHAPTER 9

Summary

SUMMARY

This thesis is about clinical quality audits, used to measure and improve the quality of health care; focusing on the quality of breast cancer care (see: the NBCA) and on the quality of breast implant surgery (see: the DBIR) in the Netherlands.

Evaluation and improvement of the quality of care is of crucial importance in the daily clinical practice, in health insurance and in policymaking. Different tools have been developed to monitor the quality of care, including regulatory inspections, surveys of consumers' experiences, internal assessments and clinical audits.[1] A clinical quality audit is a quality improvement process that seeks to improve patient care and outcomes through a systematic review of care against explicit criteria or standards, established using the principles of evidence-based medicine.[2] The goals of clinical quality audits, in general, are to increase the knowledge about diseases, to improve awareness and understanding of disease and treatment practices and it is an important tool in connecting networks of clinical expertise.

With funding from the Dutch Ministry of Health, the Association of Surgeons of the Netherlands (ASN) proceeded to develop the first national clinical quality audit in the Netherlands in 2009: the Dutch Surgical Colorectal Audit (DSCA).[3] Subsequent to the success of the DSCA, the Dutch Institute of Clinical Auditing (DICA) was founded in 2011 with the objective to facilitate the start-up of new nation-wide clinical audits in the Netherlands.[4] Concurrently, the Dutch Health Care Inspectorate observed a high rate of tumor-positive margins after breast-conserving surgery in a number of hospitals in the Netherlands, which confirmed the need for a national audit for the monitoring of the quality of breast cancer care.[5] In 2011, the NABON Breast Cancer Audit (NBCA) was instituted as a nation-wide audit to address the quality of breast cancer care in the Netherlands.[6] Meanwhile, more than 100.000 newly diagnosed patients treated for breast cancer have been registered. And within 7 years auditing, multiple processes and outcome measures (quality indicators) that cover different aspects of the multidisciplinary care path for breast cancer patients have been evaluated in order to examine improvement. Subsequently, new audit initiatives and quality assurance programs for other diseases have been developed and rapidly emerging in the Netherlands (21 audits facilitated by DICA today including the DBIR).[7]

Part I: Quality assurance in breast cancer care; the NABON breast cancer audit (NBCA)

Breast cancer is the most common cause of cancer among women. In the Netherlands over 15.000 women get diagnosed with breast cancer every year.[8] Over the past decades, many refinements of treatment modalities have been widely implemented in the field of breast cancer. In order to monitor the quality of the delivered breast cancer care, the NBCA audit was founded by clinicians of different disciplines involved in breast cancer.

In **chapter 2**, we focused on trends in the use of Neoadjuvant Chemotherapy (NAC) in breast cancer treatment. Chemotherapy is timed either prior to or following surgery, respectively neoadjuvant (NAC) or adjuvant (AC), both leading to similar disease-free and overall survival.[10,11] Chemotherapy intents to eliminate potential existing micro metastases, thus decreasing recurrence rates and mortality.[9]

NAC has several benefits compared to AC. Firstly, NAC aims to downsize the tumour to improve the possibility of a radical resection or to enable breast conservation surgery.[12,13] Another benefit of NAC includes the opportunity to de-escalate surgical treatment of the axilla.[14,15] Other potential advantages of NAC include the opportunity to investigate tumor biology, to monitor response and adapt to suboptimal response. Moreover, it is demonstrated that NAC, when compared to adjuvant chemotherapy, may even improve survival in triple-negative and HER2 positive BC subtypes when a pathological complete response (pCR) is achieved.[16]

In accordance with international guidelines, the Dutch national breast cancer guideline recommends NAC for patients with stage III BC aged <70 years. From 2011 to 2015, a high consistent rate of NAC (77%) was observed in our population of women aged 18-70 years with stage III BC, However, inter-hospital variation in the rate of NAC use was noticed varying between 0 % to 100%. We found the following predictive patient and tumour factors for the use of NAC in patients with breast cancer: young age, large tumour size, advanced nodal disease, and a negative hormone receptor status. After adjustment for these predictive factors known, the variation between the 89 Dutch hospitals remained, which indicates other potential factors of influence. Of notice, we

observed a significantly higher use of NAC in hospitals participating in neoadjuvant clinical studies (83% versus 73%).

In **chapter 3,** we evaluated the opinion of surgical and medical oncologists on the use of NAC for breast cancer. Clinicians (70 surgical and 68 medical oncologists) participating in breast cancer care in the Netherlands completed a 20-question online survey on the influence of patient, disease, and management related factors on their decisions towards NAC. NAC was recommended for locally advanced breast cancer according to most of the clinicians (94%). Despite the willingness to downstage (75%), only 64% of clinicians stated that they routinely recommended NAC when systemic therapy was indicated preoperatively. Concerns that prevented clinicians from recommending NAC are: comorbidities, age >70 years, and WHO-performance status ≥ 2. Opinions on surgical management after NAC were inconclusive; while 75% recommends NAC to enable BCS, some stated that BCS after NAC increases the risk of a non-radical resection (21%), surgical complications (9%) and recurrence of disease (5%).

In **chapter 4**, we gain insight into patients' experiences with decisions on the timing of chemotherapy. A 35-item online questionnaire was distributed among female patients (age>18) treated with either NAC or AC for stage II and III breast cancer, and almost 400 responded. Outcome measures were the experienced exchange of information on the possible choice between both options and patients' involvement in the final decision on chemotherapy timing. The need to make a treatment decision on the timing of their chemotherapy (NAC or AC) was found to be made explicit in only a small number of adjuvant treated patients, in particular in breast cancer stage II. Less than half of the respondents felt they had a real choice.

In **chapter 5**, we analyzed trends in the use of neoadjuvant chemotherapy (NAC) and the impact on surgical outcomes (in terms of positive margins and re-operations). Between 2011 and 2016, the use of NAC in the Netherlands increased from 9% to 18%. Coinciding with this trend, we demonstrated that NAC increases the rates of breast-conserving surgery (BCS) for all stages of breast cancer from 43% in 2011 to 57% in 2016. The overall positive margin rate in our study is 6,9% for 'BCS after NAC' compared to 3,3% for 'primary BCS', leading to a re-operation rate of 6,6% in 'BCS after NAC' and 5,3% in 'primary BCS'. Moreover, this nationwide data showed that

'BCS after NAC' compared to 'primary BCS' results in equal surgical outcomes for cT2 invasive breast cancer and improved surgical outcomes for cT3 invasive breast cancer. In view of the trend towards de-escalation of surgical treatment in selected patients with an excellent pathologic response, these promising results confirm that clinicians are increasingly able to perform 'BCS after NAC'.

In **chapter 6**, we evaluated the management of axillary lymph-node positive breast cancer in the Netherlands. Axillary lymph node management in breast cancer patients has changed dramatically during past decades. Previously, performing an axillary lymph node dissection (ALND) was the standard of care for all non-metastatic breast cancer patients. However, ALND is associated with a significant risk of complications such as arm swelling (lymphedema), pain, restricted shoulder movement, and sensory changes in the arm and hand.[17,18] In the early 90s, sentinel lymph node biopsy (SLNB) was introduced as an accurate and less invasive axillary staging procedure, omitting the need for ALND in early-stage sentinel lymph node-negative breast cancer patients.

Since the publication of the results of the ACOSOG-Z0011 and AMAROS trial, omitting a ALND in sentinel node-*positive* breast cancer patients is proposed in selected patients.[19,20,21,20] The results of these trials are illustrated by the 2012 Dutch breast cancer guideline, suggesting omission of ALND in cT1-2N0 breast cancer patients with a maximum of two positive sentinel nodes treated with breast conserving treatment and adjuvant systemic therapy.[22]

Between 2011 and 2015, the use of sentinel lymph node biopsy as definitive axillary staging increased from 92% to 98% for all breast cancer patients. ALND as definitive axillary staging decreased from 24% to 6%. This decreasing trend in the numbers of ALNDs for *all* tumour stadia might reflect the growing experience and the confidence among clinicians in the Netherlands towards less extensive axillary surgery of sentinel node-positive breast cancer.

Part II: Quality assurance in breast implant surgery; the Dutch Breast Implant Registry (DBIR)

Breast augmentation is the most commonly performed surgical procedure in plastic surgery worldwide. Most of the procedures performed are for cosmetic purposes, a smaller part for breast reconstructive reasons. In the Netherlands, approximately 3.3% of all mature women have breast implants.[23]

Although the use of breast implants is generally considered to be safe, breast implants are associated with short- and long-term complications, such as infection, implant rupture or deflation, late seroma, and capsular contracture.[24,25,26] In particular, implant scandals from the Dow-Corning crisis in the 1980s to the more recent PIP crisis have raised public awareness.[27] Recently, an association between breast Anaplastic Large Cell Lymphoma (ALCL) has been found.[28,29] Furthermore, it has been suggested that there is an association between autoimmunity and silicon exposure resulting in ASIA (autoimmune/inflammatory syndrome induced by adjuvants) and various autoimmune diseases.[30,31,32]

In response to these emerging safety concerns, several national societies around the world developed breast devices registries of which six up and running registries today, including the Australian Breast Device Registry (ABDR),[33] the Bröstimplantatregistret of Sweden (BRIMP),[34] the Austrian Breast Implant Register (ABIR),[35] the Breast and Cosmetic Implant Registry of the United Kingdom (BCIR),[36] the US National Breast Implant Registry (NBIR)[37], and the Dutch Breast Implant Registry (DBIR).[38]

The DBIR registry was founded in 2015, with the objective to facilitate and organize the initiation of nationwide breast implant-related outcome measures in the Netherlands. A unique feature of the DBIR is its opt-out construct, without the need for informed consent. The national coverage has been assessed by comparing the number of institutions in DBIR to the number of eligible institutions known by the Dutch Health and Youth Care Inspectorate (IGJ). In the first full registration year (2016), the participation rate was 95% for hospitals and 78% for private clinics.

In **chapter 7**, we provide an overview of early outcomes and experiences of the DBIR registry. Between 2015 and 2017, a total of 15,049 patients and 30,541 breast implants

were included. A minimum incidence rate of 1 implant per 1,691 women in 2017 could be determined. The majority of devices was inserted for a cosmetic indication 26,036 (85.2%), and 4,505 (14,8%) for a breast reconstruction. In general, patient, device and surgery characteristics differed per indication group. Patients who underwent cosmetic breast augmentation were younger than breast reconstruction patients (31,5 versus 49,7 years of age). Between 2016 and 2017, a decrease in the use of textured implants was seen in both indication groups. Furthermore, in the reconstructive group, an increase of the use of round implants and silicone filled implants was found, with appears to coincide with the critical issue of breast implant-associated ALCL.

Another preliminary finding is the differences between hospitals in the use of four selected perioperative infection control measures (all ranged 0-100%). Overall, an increased use was shown of prophylactic intravenous antibiotics, gloves change before the insertion, and in the rinse of a breast implant with an antiseptic solution. The use of drains decreased in reconstructive procedures but increased in cosmetic augmentations. Long-term clinical data will eventually reveal the actual health effects of intraoperative techniques and antiseptic precautions.

In the final part of this thesis, **chapter 8**, we have outlined the process undertaken by the International Collaboration of Breast Registry Activities (ICOBRA). ICOBRA is an international multidisciplinary group with expertise in breast device registries including consumer representatives, national regulators, and biostatisticians, and were gathered to develop a standardized global minimum dataset for breast implant registries. Data points from the six up and running national breast implant registries were compared. Secondly, a modified Delphi approach was used, with surveys requiring the panellists to rate the importance of each data point to be included in the global minimum data set. After four survey rounds, a consensus was reached on a list of 32 data points to be included in the global core dataset. Data points for which consensus was not achieved (16 data points), were not voted into the core set and became the optional dataset. Consensus on definitions for all data points was achieved using the definitions of the Australian dataset as the starting point. The ICOBRA core- and optional dataset is almost completely integrated into the DBIR dataset. It is expected that the global dataset will be adopted by currently operating breast device registries within two years and by all new breast implant registries in the ICOBRA network (including Australia,

Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, the United Kingdom, and the United States). The ICOBRA global dataset will allow pooling data from breast implant registries in order to evaluate active surveillance and comparative outcomes. This will safeguard the health of recipients of breast implants by preventing implantation of under-performing devices.

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CHAPTER 10

General Discussion and Future Perspectives

GENERAL DISCUSSION

There are several reasons why national clinical quality audits can and should help us in the provision of good quality of care:

1. *Quality Assurance and Patient Safety:* Participation in quality improvement initiatives, with continuous quality measurement and benchmarked feedback of data, reveals opportunities to improve health care, decreases unintended variation and eventually might improve the value of healthcare delivery.[1,2]
2. *Scientific importance:* The outcomes of 'real world' medical practice data are becoming of increasing practical and scientific importance.[3] By using nationwide clinical data, the actual applicability of important findings of biomedical and clinical research can be evaluated according to daily practice.
3. *Shared decision making:* Patients want to know the quality of care they are about to receive. And, shared decision making is becoming increasingly important in achieving patient-centered care. Dynamic clinical data mining can be used to provide real-time decision support.[4]
4. *Cost-effectiveness*: Health care systems costs in developed countries are rising, in part due to the introduction of advanced medical technology, pharmaceutical disbursement as well as growing cancer burden.[5] Clinical audits can function as a quality instrument to increase the efficiency of care, and therefore as a tool to reduce costs.[6]

Quality assurance in breast cancer care

The main purpose of a national clinical quality audit is to provide healthcare providers with reliable, benchmarked information on structure, process and outcome parameters. We have shown that the NABON Breast Cancer Audit (NBCA) has reached that goal and is continuously working on exploring this purpose even more.[7] In five years' time, all hospitals reached the predefined standards for the management of breast cancer in the Netherlands; e.g. 'more than 90% of patients being discussed in the multidisciplinary meetings', 'more than 90% of patients with a standard defined pathology report', and 'less than 15% of patients with involved margins for invasive breast cancer'. This demonstrates that guideline adherence has been improved and a multidisciplinary approach is widely adopted in the Netherlands.

Producing meaningful quality indicators that inform clinicians is essential in the support of benchmarked feedback. The current quality indicator set of the NBCA predominantly consists of quality process indicators, covering different aspects of the multidisciplinary care path for breast cancer patients, from diagnostic work-up to different treatment options. Two types of quality process indicators can be distinguished: **I.** Quality indicators that measure compliance with clinical guidelines with the aim to improve adherence to guidelines and reduce variation in delivered care **II.** Quality indicators that monitor the implementation of new treatment modalities and techniques, where variation is expected.

Figure 1 shows examples of different quality process indicators and their trends in time, indicating the relevance of a particular indicator for quality improvement. An increase or decrease on a nationwide level on a quality indicator represents its adoption as a component in the multimodality care of breast cancer. In addition, decreasing inter-hospital variation reflects the process of implementation.

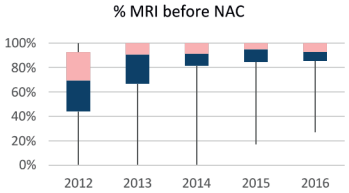

Figure 1A. The use of Magnetic Resonance Imaging – scan (MRI) before the start of Neoadjuvant Chemotherapy (NAC) in invasive breast cancer; an upward trend ↑ and decreasing variation ↓.

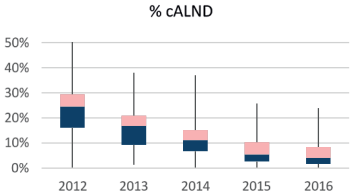

Figure 1B. The use of a completion axillary lymph node dissection (cALND) in cT1-2N0* sentinel node-positive breast cancer; a decreasing trend ↓ and decreasing variation ↓.

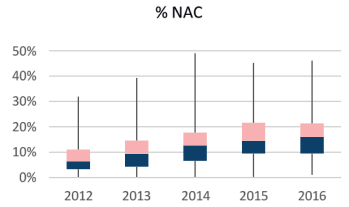

Figure 1C. The use of Neoadjuvant Chemotherapy (NAC) in invasive breast cancer; an upward trend ↑ and a constant range of variation X.

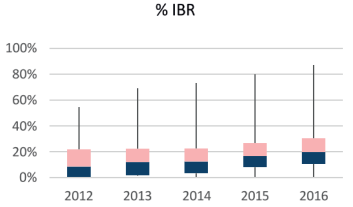

Figure 1D. The use of immediate breast reconstruction (IBR) in invasive breast cancer; an upward trend ↑ and a constant range of variation X.

Examples of *Type I indicators* are a. 'the use of a Magnetic Resonance Imaging scan (MRI) before the start of Neoadjuvant Chemotherapy (NAC)' and b. 'the omission of a completion axillary lymph node dissection (ALND) in clinical early-stage sentinel node-positive breast cancer patients'. Both these indicators are based on clear recommendations in the Dutch guideline. An upward (1A), respectively downward (1B) trend in combination with decreasing variation is shown, representing an improvement of guideline compliance for both the use of MRI before NAC as well as the omission of ALND in patients with a positive sentinel node.

In figure 1 c and d, 'the use of NAC' and 'the use of immediate breast reconstruction (IBR) after mastectomy' in invasive breast cancer –are depicted as examples of *Type II indicators*; as evidence from research studies has not yet been included in the national guideline. Despite an upward trend on a nationwide level, the routine of application of these modalities remains different between hospitals; as being shown by a persisting wide variation.

Although the general trend in breast cancer treatment in the Netherlands shows an improvement of the quality of care and a rapid adaptation of new study results, transparency on inter-hospital variation may increase the exposure to new approaches, in particular for treatment modalities without a set standard (yet). Where national guidelines are rigid, feedback from clinical audits could be interpreted as a 'dynamic guideline' that provides new insights and reduces unintended clinical practice gaps.

Today, the challenge of the NBCA is to move beyond a national benchmark mainly centered on process information to a national breast cancer audit centered on outcomes, including composite measures and patient-reported outcomes (PROMs), that visualizes the actual results of care. This approach is complex, and can only occur with continuous evaluation of the given quality indicators, and to redefine and test potential new quality indicators with the support of data over time. In the meantime, quality process indicators may still be relevant in improving the more rapid implementation of innovates.

Scientific importance

Furthermore, a national clinical quality audit provides complete information on clinical care and outcomes, with the inclusion of patients that do not fit within the inclusion criteria of clinical trials. The database of the NBCA consists of an amount of data and any person or hospital who is involved in the NBCA audit can submit a research question. This has led to a scale of scientific research, of which the most important studies are shown in **table 1**. In particular, nationwide studies on the use of MRI, the use of neoadjuvant systemic treatment, surgical management of the breast, axillary lymph-node management, the prognostic value of the 70-gene signature (70-GS) and the use of boost irradiation have been conducted.

This thesis includes the results of one of the largest nationwide studies demonstrating a trend of more breast-conserving surgery (BCS) after NAC (chapter 5). Moreover, this study confirms that clinicians in the Netherlands are increasingly able to perform 'BCS after NAC' while maintaining good surgical outcomes (including margins and re-excision rates), compared to primary BCS.

Another notable finding in this thesis is the downward trend in the use of an axillary lymph node dissection (ALND) in cT3-4N0M0 sentinel node-positive breast cancer patients (chapter 6). While no randomized trials have been published before to justify less extensive axillary surgery in this group of patients, this study reflects the confidence of clinicians in the concept that not every positive axillary sentinel lymph node will develop into clinical detectable axillary disease.

Though these are promising results, however, the reliability of this developmental data is limited by the retrospective nature and missing data on follow-up. Therefore, we recommend that future research should include epidemiological sound data and patient-reported outcomes (e.g. quality of life, functional and cosmetic outcomes), in order to provide more meaningful outcomes that matter to patients.

Table 1. Studies on trends and causes of inter-hospital variation, supported by NBCA data (2015-2018)

Discipline		Publications
Radiology	1	M.B.I. Lobbes. *Breast MRI increases the number of mastectomies for ductal cancers but decreases them for lobular cancers.*
	2	I.J.H. Vriens. *Breast MRI use in patients undergoing NAC is associated with fewer mastectomies in large ductal cancers but not in lobular cancers.*
Surgery	3	P.E.R. Spronk. *Breast-conserving therapy after neoadjuvant chemotherapy; data from the Dutch Breast Cancer Audit.*
	4	I.G.M. Poodt. *Trends on Axillary Surgery in Nondistant Metastatic Breast Cancer Patients Treated Between 2011 and 2015. A Dutch Population-based Study in the ACOSOG-Z0011 and AMAROS Era.*
Plastic Surgery	5	A.C.M. van Bommel. *Large variation between hospitals in immediate breast reconstruction (IBR) rates after mastectomy for breast cancer in the Netherlands.*
	6	K. Schreuder. *Hospital organizational factors affect the use of IBR after mastectomy for breast cancer in the Netherlands.*
	7	K. de Ligt. *The effect of being informed on receiving IBR in breast cancer patients.*
	8	A.C.M. van Bommel. *Discrepancies between surgical oncologists and plastic Surgeons in patient information provision and personal opinions towards IBR.*
Radiotherapy	9	K. Schreuder. *Variation in the use of boost irradiation in breast-conserving therapy in the Netherlands: The effect of a national guideline and confounding factors.*
Systemic	10	A. Kuijer. *Using a gene expression signature when controversy exists regarding the indication for adjuvant systemic treatment reduces the proportion of patients receiving adjuvant chemotherapy.*
treatment	11	A. Kuijer. *Factors Associated with the Use of gene-expression profiling (GEP) in Estrogen Receptor-Positive Early-Stage Breast Cancer Patients.*
	12	K. Schreuder. *Impact of GEP in patients with early breast cancer, when applied outside the guideline, directed indication area.*
	13	P.E.R. Spronk. *Variation in the use of neoadjuvant chemotherapy in patients with stage III breast cancer: results of the Dutch Breast Cancer Audit.*
	14	P.E.R. Spronk. *Current decisions on neoadjuvant chemotherapy for early breast cancer: Experts' experiences in the Netherlands.*
	15	I.G.M. Poodt. *The administration of adjuvant chemo(-immuno) therapy (AC) in the post ACOSOG-Z0011 era; a population-based study.*
	16	K. de Ligt. *Patients' experiences with decisions on timing of chemotherapy for breast cancer.*

Shared decision making

Multiple determinants might attribute to unintended inter-hospital variation;

- patients' preferences
- clinicians' preferences
- the organizational context

An example of a treatment modality without a predefined standard is the use of neoadjuvant chemotherapy (NAC) for breast cancer. Despite an international trend of increasing implementation for NAC, considerable variation in the use of NAC remains between hospitals [this thesis].

Patients' preference

Where in earlier years the patient was happy with a doctor who decided the best treatment plan; nowadays, patients' preference and the level of shared decision-making are important factors in clinical decision making, especially in breast cancer care. There are multiple factors affecting patients' considerations, including information related to treatment efficacy and toxicity, prior experience with the treatment, quality of life during or after treatment, opinion of their care provider and of partner or family preference.[13] However, as described in chapter 4, the results of our study revealed that the need to make a treatment decision on NAC was found to be made explicit in only a small number of patients, and there remains room for improvement in the delivery of shared-decision making.

Clinicians' opinions exert one of the most powerful influences over patients' preferences.[14] In order to meet the needs of patients with cancer and their families, the system should be oriented to the provision of 'patient-centered care'. As defined by the Institute of Medicine: *"Patient-centeredness is providing care that is responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions"* [15]. As a component of patient-centered care, structured decision aids have been advocated to help patients become active participants in making treatment choices.[16] In the future, NBCA data may contribute to providing more individualized information about treatment options.

Clinicians' preferences

Whether a patient is a candidate for chemotherapy (NAC or AC) depends on multiple factors; e.g. our ability to preoperatively estimate the change on a pathological complete response. The results of our survey among specialists confirm that clinicians' considerations on NAC differ significantly (chapter 3). In particular opinions on the surgical management following NAC were inconclusive. The restraint to perform BCS after NAC may arise from the challenge for surgeons to determine the extent and original location of the residual lesion after NAC. Another possible contributing aspect is the concept of accessibility and proximity.[8] Similar to other choices made with equivocal information, clinicians may satisfice by choosing an advice source who is known. Again, this highlights the importance of continuous up-to-date feedback on new treatment modalities.

The organizational context

Non-clinical influences may play an important role either in the adoption of new treatment modalities; such as the interaction within a professional community and features of clinical practice such as local management policies. Clinicians are more likely to be early adopters if they are actively involved in the medical community.[9,10] It creates more awareness among physicians and it narrows the gap between the best available evidence and current practice. Of notice, we observed a significantly higher use of NAC in hospitals participating in neoadjuvant clinical studies [this thesis]. Also, companies can influence physicians in certain ways; for example by arranging interaction with a pharmaceutical representative, funding physicians for travel or attending educational symposia as well as providing research funding.[11,12]

Quality assurance and Patient safety in breast implant surgery

Breast implants are routinely used for breast augmentation. In the Netherlands, an estimated of more than 11.000 implants are annually inserted for cosmetic reasons.[17] Moreover, improved outcomes of breast cancer have resulted in a growing number of breast cancer survivors, who choose for reconstructive surgery of the breast following mastectomy.[18,19] Implant-based breast reconstruction is the most commons means of reconstructive surgery. Compared to a reconstruction with autologous tissue, the advantages of and implant-based breast reconstruction are the short operative time, lack of donor-site morbidity, and quicker return to normal life activities.[20] According to the NBCA audit, an estimate of 10% of patients with invasive breast cancer received a mastectomy followed by an immediate breast implant reconstruction in the Netherlands in 2016.[21]

Despite the increase in implant procedures, there are currently no reliable or epidemiologically sound data to measure implant performance. Therefore, the main purpose of the Dutch Breast Implant Registry (DBIR), founded in 2015, is to provide sufficient data on breast implant surgery, to address potentially serious complications such as implant removal, reoperation, and rupture or deflation of the implant. Moreover, the registry can be used as a track-and-trace system in case of an implant recall. Patients with the implant(s) of interest can be identified and hospitals can be addressed to prevent further implantation of faulty devices. An example of this is the recent withdrawal from the market of Silimed implants after German health officials found that the surfaces of some devices were contaminated with unknown particles.[22] In general, a medical device cannot be marketed in Europe without carrying a certificate of conformity. After this report became known, within a few hours the number of Silimed implants in the Dutch Breast Implant Registry could be determined, thereby providing clarity for patients and institutions.

Scientific importance

In addition, in the absence of high-quality, randomized controlled trials to assess the effect of various intraoperative techniques on surgical and cosmetic outcomes, data of the national DBIR registry provide a pragmatic alternative source of evidence. For example, previous studies suggest that the risk of capsular contracture is reduced when implants are placed in a subpectoral position, or if an inframammary surgical incision is

used instead of an areolar incision.[23,24] However, most of these studies are biased due to treatment by indication, loss of follow-up and lack information on potential risk factors as the effect of the implant itself. Simultaneously, unexplained variation between hospitals in the use of antiseptic precautions (antibiotics, antiseptic rinse, glove change prior to implant handling and the use drains) has been observed. [this thesis].

Most importantly, epidemiologically data will reveal the actual health effects of breast implants in relation to breast implant-associated Anaplastic Large Cell Lymphoma (BIA-ALCL) and/or potential other long-term adverse outcomes. BIA-ALCL is a rare cancer of the immune system believed to be causally associated with textured breast implants.[25,26] So far, various, not mutually exclusive causal factors have been suggested. Specifically, a local inflammatory response, elicited by silicone derived products or specific bacterial species adherent to the prosthesis surface (biofilm). In our DBIR data, between 2016 and 2017, a significant decrease in the use of textured implants and an increase in the use of smooth implants was observed already, that appears to coincide with the critical issue of BIA-ALCL [this thesis].

International collaborations

It is important that quality improvement initiatives are aligned as much as possible. Harmonization of indicator sets, data points, and data definitions is key to eventually pool and compare data from different clinical audits. The process undertaken by the International Collaboration of Breast Registry Activities (ICOBRA) in which they developed a standardized global minimum dataset for breast implant surgery, is an attempt in achieving this goal [this thesis]. Importantly, the use of large pooled international datasets is the only way we can address adverse events with a low incidence. In addition, an international approach can help in the exchange of information on practical hurdles that will be faced when starting a clinical quality audit; including (1) funding, (2) medical ethical issues, (3) privacy and legal issues (4) compliance (5) dataset and registry principles (5) benchmarking and output (6) quality assurance, data governance and research.[27,28]

FUTURE PERSPECTIVES

The NABON Breast Cancer Audit has been useful by serving as a platform for initiatives of quality improvement in breast cancer care in the Netherlands. The Dutch Breast Implant Registry (DBIR) is one of the first up-and-running breast implant registries worldwide, and the result of an international collaborative and conjoint effort by the ICOBRA network. Now that a sound foundation for quality assurance in breast cancer care and breast implant surgery has been laid, further national and global initiatives should be taken towards a common interconnecting registration system for multiple purposes.

Interconnecting data systems

Access to a vast volume of data, to identify and collect identifiable information on best practices, will contribute to individualized strategies for diagnostic or therapeutic decision-making. However, several challenges with data in healthcare have yet to be addressed; the technical expertise required to pool data, a lack of robust integrated security surrounding it, and a joint venture between facilitating companies in the field of health care monitoring. A. A patient-centered system will not be able without the involvement of all disciplines in the multidisciplinary pathway of care. B. A connection of clinical audits to other data systems is fundamental in order to move beyond a linear data structure to a multidimensional model. It would not only create an enormous resource for outcome research, but it may also support prescriptive modeling in order to more effective diagnosis and treatment.[32,33]

Patient-centered care

The use of Patient-Reported Outcome Measures (PROMs); reports and ratings provided by patients or their proxies about their health, functioning, health behaviors and quality of care, is set to rise in clinical and research setting.[29] It can be used for screening early symptoms or side effects of treatments, monitoring outcomes meaningful to patients, and most importantly, improves communication at the individual level. Their use in clinical practice helps to ensure the patient 'voice' is present during the consultation and evaluation of treatment, and may help in better patient-physician dialogues. In 2016, a global standard set of value-based patient-centered outcomes for breast cancer was developed by the International Consortium for Health Outcomes

Measurement (ICHOM), a multidisciplinary international working group comprised of patient advocates and health care providers, including members of the Dutch Institute for Clinical Auditing (DICA) and NBCA scientific committee.[30] This standard breast cancer set consists of outcomes of almost a full cycle of breast cancer care, with an emphasis on patient-reported outcomes.

In-hospital health care programs

Health care providers are increasingly incorporating clinical auditing into daily practice, and that is changing perspectives into how to make care more efficient and valuable. An example of a quality improvement program is the 'Santeon Value-Based Health Care Program', a conjoint effort of seven teaching hospitals across the Netherlands that use benchmarked information on the process, outcomes, and costs, including the use of the ICHOM breast cancer set.[31] The strength of this collaboration lies in its set-up in which a 'quality improvement team' is assigned per hospital (consisting of a project manager, data manager, data analyst). As a result, expertise on clinical auditing is not limited to a national audit board, but an in-hospital clinical team creates a sustainable base for continued implementation of quality culture improvement activities. In addition, the implementation of the 'Codman dashboard', an application from DICA that provides dynamic feedback on process and outcomes of data per hospital, will increase the use of clinical audits in daily practice even more.[35]

Cost-effectiveness

Beyond the scope of this thesis, a national clinical quality audit can also function as a tool to reduce costs.[6] Medical innovation has delivered significant improvements in clinical care, but the changes in healthcare are also reflected by the expenditure in healthcare costs.[36] And, the fact is that we are faced with an aging population and the demand for care will only increase. As raised by Michael E. Porter, the overall goal in healthcare should be maximizing value for patients.[37] An opportunity to improve insight in the efficiency and value of healthcare is the introduction of more accurate cost calculations when evaluating care processes. As seen in the study of Govaert et al. in which they investigate whether improvements in surgical colorectal cancer care leads to a reduction of hospital costs, the reduction of complications or other undesired outcomes is undoubtedly beneficial to patients and reduces costs.[38]

CONCLUSION

The results of this thesis show that clinical audits as The NABON Breast Cancer Audit (NBCA) and The Dutch Breast Implant Registry (DBIR) have the potential to provide quality assurance and further extensive outcome research. Several important nation-wide trends on breast cancer treatments and breast implant surgery are described, what no randomized trials have been published before. Furthermore, data from clinical audits can be used for clinical decision-support systems and may support broader health care effectiveness research. Future quality initiatives should focus on (international) collaborations and sharing data, which may help to improve the quality of care in a more efficient and focused manner.

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CHAPTER 11

Dutch Summary

Curriculum Vitae

Author's list of publications

Acknowledgements

SAMENVATTING

Landelijke kwaliteitsaudits dienen ter ondersteuning van kwaliteitsverbetering van zorg in Nederland. In dit proefschrift worden de resultaten beschreven van twee belangrijke landelijke kwaliteitsaudits op het gebied van borstkankerzorg (de NBCA) en borstimplantaatchirurgie (de DBIR).

Het meten en evalueren van de kwaliteit van geleverde zorg is van cruciaal belang om zorg te kunnen verbeteren. Deze kwaliteitsinformatie wordt tevens gebruikt ter ondersteuning van beleidsvorming in de gezondheidszorg en voor zorginkoop door zorgverzekeraars. Er zijn diverse instrumenten ontwikkeld om de kwaliteit van zorg meetbaar te maken; o.a. enquêtes onder consumenten, inspecties vanuit de overheid, interne audits, en dus zogenaamde landelijke '*kwaliteitsaudits*'.[1] Een kwaliteitsaudit is een systematische methode, waarbij het proces en de uitkomsten van zorg op landelijk niveau worden geëvalueerd aan de hand van vooraf vastgestelde standaarden (kwaliteitsindicatoren), welke voornamelijk zijn gebaseerd op 'evidence-based medicine'.[2] In het algemeen is het doel van een kwaliteitsaudit om expertise samen te brengen en hierdoor kennis over ziekten en behandelingen te vergroten.

Middels financiering vanuit het Nederlandse Ministerie van Gezondheidzorg (VWS), werd door de Nederlandse Verenging van Heelkunde (NvvH) in 2009 de eerste landelijke kwaliteitsaudit ontwikkeld: the Dutch Surgical Colorectal Audit (DSCA).[3] In 2011 werd 'the Dutch Institute of Clinical Auditing' (DICA) opgericht om de oprichting van nieuwe landelijke kwaliteitsaudits in Nederland te kunnen blijven faciliteren.[4] In deze periode werd tevens een alarmerend rapport gepubliceerd vanuit de Inspectie van de Gezondheidszorg over de verschillen in borstkankerzorg in Nederland.[5] Vanuit het Nationaal Borstkanker Overleg Nederland (NABON) werd een werkgroep geformeerd en nog in hetzelfde jaar werd de NABON Breast Cancer Audit (NBCA) opgericht.[6] Inmiddels zijn er gegevens van meer dan 100.000 borstkankerpatiënten geregistreerd, kwaliteitsindicatoren geëvalueerd en doorontwikkeld, en kwaliteit-verbeterinitiatieven in ziekenhuizen ondersteund middels de data uit de NBCA. Ook andere landelijke kwaliteitsaudits voor uiteenlopende oncologische en niet-oncologische ziektebeelden ontwikkelen zich in snel tempo (vandaag de dag telt DICA 22 kwaliteitsaudits, inclusief de Dutch Breast Implant Registry).[7]

Deel I: Kwaliteitsborging borstkankerzorg; de NABON Breast Cancer Audit (NBCA)

Borstkanker is de meest voorkomende oorzaak van kanker bij vrouwen. In Nederland krijgen elk jaar meer dan 15.000 vrouwen de diagnose borstkanker.[8] Er hebben in de afgelopen decennia enorme ontwikkelingen plaatsgevonden op het gebied van de behandeling van borstkanker. Om de kwaliteit van de geleverde borstkankerzorg te kunnen blijven bewaken, werd door een groep vertegenwoordigers van verschillende disciplines betrokken binnen de behandeling van borstkanker de NBCA-audit opgericht.

In **hoofdstuk 2** hebben we ons gericht op trends in het gebruik van Neoadjuvante Chemotherapie (NAC) binnen de behandeling van borstkanker in Nederland. Chemotherapie kan zowel vóór als na de operatie worden toegepast, respectievelijk Neoadjuvant (NAC) of Adjuvant (AC), beide leidend tot vergelijkbare cijfers betreft ziektevrije en totale overleving.[10,11] Het doel van chemotherapie is om mogelijke nog bestaande micro-metastasen te elimineren en hierdoor de kans op een recidief te verminderen.[9]

Echter, het toepassen van NAC (chemotherapie voorafgaand aan de operatie) heeft voordelen ten opzichte van AC. Ten eerste leidt het gebruik van NAC tot zogenaamde 'downstaging'; het verkleinen van de tumor. Hierdoor kan uiteindelijk vaak borstsparend geopereerd worden, terwijl in eerste instantie een mastectomie (het verwijderen van de gehele borst) zou zijn geïndiceerd.[12,13] Een ander voordeel van NAC is 'downstaging' van mogelijke uitzaaiingen naar de lymfklieren in de oksel.[14,15] Bovendien is er aangetoond dat NAC, in vergelijking tot AC, de ziektevrije overleving kan verbeteren voor bepaalde subtypen van borstkanker (respectievelijk triple-negatieve en/of HER2-positieve borstkanker), mits er een pathologische complete respons na NAC wordt bereikt.[16] Een ander potentieel voordeel van NAC is de mogelijkheid om de tumorbiologie 'in vitro' te onderzoeken. De respons op chemotherapie kan hierdoor worden geanalyseerd en het chemotherapieschema kan worden aangepast indien er sprake is van een suboptimale respons.

Volgens de Nederlandse richtlijn voor borstkanker is NAC geïndiceerd bij patiënten jonger dan 70 jaar oud met stadium III borstkanker (een tumor >5cm en eventuele

uitzaaiingen naar de lymfeklieren in de oksel). Dit is conform de aanbevelingen van internationale richtlijnen.

Het landelijke gemiddelde aan NAC voor stadium III borstkanker is van 2011 tot 2015 in Nederland nauwelijks veranderd, met een consistent percentage van gemiddeld 77%. Echter, een aanzienlijke variatie in de toepassing hiervan tussen ziekenhuizen [van 0 tot 100%] suggereert dat er sprake is van een onderbenutting van NAC in Nederland. Factoren die samenhingen met het krijgen van deze behandeling waren: een jonge leeftijd, de tumorgrootte, het aantal positieve lymflieren en de (negatieve) hormoonreceptorstatus. Ook een multidisciplinaire preoperatieve samenwerking tussen zorgverleners en deelname aan klinische trials bleken het gebruik van NAC te beïnvloeden. Grote verschillen tussen ziekenhuizen bleven echter aanwezig na correctie van deze case-mix. De conclusie luidt dan ook dat slechts een deel van de aangetroffen variatie tussen ziekenhuizen in Nederland in het toepassen van NAC is toe te schrijven aan patiënt- of tumorkenmerken.

Om beter inzicht te krijgen in de achterliggende oorzaken van variatie en om de bewustwording bij specialisten en patiënten te verhogen, werd er vervolgonderzoek geïnitieerd, zoals beschreven in hoofdstuk 3 en 4. In **hoofdstuk 3** onderzochten we de mening van chirurgen en medisch oncologen ten aanzien van NAC. In totaal waren er 138 specialisten (70 chirurgen en 68 medisch oncologen) die een online survey voltooiden, met vragen die betrekking hadden op de invloed van patiënt-, ziekte- en managementgerelateerde factoren op de besluitvorming ten aanzien van NAC. Vrijwel elke deelnemer (94%) was het eens met de Nederlandse richtlijn; NAC is geïndiceerd voor stadium III borstkanker. Ondanks dat ook het merendeel (75%) het voordeel van 'downstaging' beaamde, adviseert 64% van de artsen NAC op stelselmatige basis wanneer chemotherapie geïndiceerd is op basis van preoperatief vastgestelde factoren. Redenen om NAC niet aan te bevelen zijn: co morbiditeit, een leeftijd >70 jaar en een WHO-prestatiestatus ≥2. Ook werden de volgende risico's ten aanzien van de chirurgie onderstreept door enkele specialisten; NAC zou het risico verhogen op: een niet-radicale resectie (21%), chirurgische complicaties (9%) en een recidief (5%).

In **hoofdstuk 4** hebben we onderzocht in hoeverre patiënten zich betrokken voelden in de besluitvorming over de timing van chemotherapie; die respectievelijk vóór (NAC)

als na de operatie (AC) toegepast kan worden. Alle 394 vrouwelijke respondenten waren >18 jaar en tussen 2013 en 2014 behandeld met NAC of AC vanwege stadium II of stadium III borstkanker. De 35 vragen hadden o.a. betrekking op de mate van informatieoverdracht, of de mogelijke keuze tussen beide opties was besproken en of de patiënt zich betrokken had gevoeld in de uiteindelijke besluitvorming. Slechts met een kleine groep respondenten die behandeld waren met AC was de mogelijkheid van NAC besproken. Dit was met name in de groep respondenten met stadium II borstkanker. Minder dan de helft van alle respondenten heeft het gevoel gehad 'dat zij de keuze over de timing van chemotherapie zelf hebben gemaakt'.

In **hoofdstuk 5** hebben we de trends in het gebruik van NAC onderzocht voor alle stadia van borstkanker en daarbij met name gekeken naar de impact van NAC op de chirurgische uitkomsten (zowel het percentage aan positieve resectiemarges als het aantal her-operaties). Het algehele gebruik van NAC is toegenomen in Nederland, met een landelijk gemiddelde van 9% in 2011 naar 18% in 2016. Tevens konden we aantonen dat NAC de mogelijkheid tot borstsparende chirurgie (BCS) voor alle stadia van borstkanker aanzienlijk heeft verhoogd; van 43% in 2011 tot 57% in 2016. Het percentage positieve resectiemarges voor 'BCS na NAC' bedroeg in onze studie 6,9%, in vergelijking tot 3,3% voor 'primair BCS'. Bovendien bevestigt onze studie dat 'BCS na NAC' in vergelijking tot 'primair BCS' resulteerde in gelijke chirurgische uitkomsten voor cT2 tumoren (tumorgrootte 2-5cm), en zelfs betere chirurgische uitkomsten voor cT3 tumoren (tumorgrootte >5cm).

Deze resultaten zijn veelbelovend gezien de tendens naar de-escalatie van de chirurgische behandeling; het minder invasief opereren of zelfs - in de toekomst - niet meer opereren indien een complete pathologische respons kan worden bereikt middels NAC. Het bevestigt dat chirurgen steeds beter in staat zijn een resectie uit te voeren na NAC.

In **hoofdstuk 6** onderzochten we trends in de behandeling van lymfeklierpositieve borstkanker, een stadium van borstkanker waarbij er uitzaaiingen naar de oksel (axilla) zijn geconstateerd. De behandeling van lymfeklierpositieve borstkanker is in de afgelopen decennia drastisch veranderd. Voorheen was het uitvoeren van een axillaire lymfeklierdissectie (ALND) een standaardbehandeling voor alle borstkankerpatiënten.

Echter, een ALND is geassocieerd met een significant risico op complicaties zoals lymfoedeem (zwelling van de arm door stapeling van lymfevocht), pijn, beperkte mobiliteit en sensorische disfunctie in de onderarm.[17,18] In het begin van de jaren '90 werd de schildwachtklierprocedure (SLNB) geïntroduceerd. Dit is een nauwkeurige en minder invasieve axillaire stadiëringsprocedure waardoor er geen noodzaak meer is voor een ALND in patiënten met een *negatieve* schildwachtklier.

Sinds de publicatie van twee belangrijke studies op het gebied lymfeklierpositieve borstkanker, de ACOSOG-Z0011- en AMAROS- trial, wordt het weglaten van een ALND geadviseerd in een geselecteerde groep aan patiënten waarbij de schildwachtklier desondanks *positief* is.[19,20]

De tienjaarresultaten van de ACOSOG-Z0011-studie (1999-2004, gepubliceerd in 2011) toonden aan dat er geen significant verschil was in locoregionale recidiefvrije overleving voor cT1-2 borstkankerpatiënten (tumorgrootte <5cm) met 1-2 positieve schildwachtklier(en), indien zij behandeld waren met BCS gevolgd door radiotherapie of indien zij behandeld waren met een ALND.[21] De AMAROS-studie (2001-2010, gepubliceerd in 2014) bevestigde dat voor cT1-2 borstkankerpatiënten met 1≤ positieve schildwachtklier de regionale controle vergelijkbaar is tussen een ALND en axillaire bestralingstherapie. Tevens gaat axillaire radiotherapie gepaard met aanzienlijk minder morbiditeit.[20] Naar aanleiding van deze resultaten adviseert de huidige Nederlandse borstkankerrichtlijn dat een ALND achterwege gelaten kan worden indien er sprake is van cT1-2 borstkanker met 1-2 positieve schildwachtklier(en) en de behandeling bestaat uit borstsparende chirurgie, radiotherapie en adjuvante systemische therapie.[22]

Het gebruik van een schildwachtklierprocedure als definitieve axillaire stadiëring is toegenomen van 92% in 2011 naar 98% in 2015, voor alle borstkankerpatiënten in Nederland. Het gebruik van een ALND als definitieve axillaire stadiëring daalde van 24% naar 6%. Deze afnemende trend in het aantal ALND's voor *alle* stadia van borstkanker is een weerspiegeling van de snelle implementatie in Nederland van deze belangrijke studieresultaten en een groeiende kennis en ervaring onder specialisten, waardoor de oksel steeds minder invasief wordt behandeld.

Deel II: Kwaliteitsborging borstimplantaatchirurgie; the Dutch Breast Implant Registry (DBIR)

Een borstvergroting is de meest uitgevoerde chirurgische ingreep binnen de plastische chirurgie, veelal uitgevoerd vanwege cosmetische redenen of vanwege de wens tot een borstreconstructie na bijvoorbeeld de behandeling van borstkanker. In Nederland heeft ongeveer 3,3% van alle volwassen vrouwen borstimplantaten.[23]

Hoewel het gebruik van borstimplantaten over het algemeen als veilig wordt beschouwd, is borstimplantaatchirurgie geassocieerd met het risico op complicaties; zoals infecties, deflatie of ruptuur van het implantaat, seroomvorming en kapselcontracturen.[24,25,26] Met name het schandaal rondom de gescheurde 'Dow-Corning borstimplantaten' in de jaren tachtig en de ophef rondom de omstreden Poly Implants Prothèses (PIP), heeft het publieke bewustzijn rondom de veiligheid van borstimplantaten verhoogd.[27] Tevens is uit recent onderzoek gebleken dat vrouwen met borstimplantaten een verhoogd risico lopen op het ontwikkelen van een anaplastisch grootcellig lymfoom (ALCL).[28,29] Ook wordt gesuggereerd dat er een verband bestaat tussen auto-immuniteit en de blootstelling aan siliconen, wat zou kunnen resulteren in het ASIA-syndroom (autoimmune/inflammatory syndrome induced by adjuvants) en verschillende auto-immuunziekten.[30,31,32]

Vanwege de onopgeloste veiligheidsvraagstukken zijn verschillende landen gestart met het opzetten van borstimplantaat-registraties. Momenteel hebben zes landen een actieve registratie: Australië (ABDR),[33] Zweden (BRIMP),[34] Oostenrijk (ABIR),[35] England (BCIR),[36] Amerika (NBIR).[37] In 2015 werd de DBIR opgericht ten behoeve van borstimplantaat-gerelateerde uitkomstmaten in Nederland.[38] Een uniek concept van de DBIR is het 'opt-out systeem', wat betekent dat de patiënt geïncludeerd is mits er voorafgaand expliciet géén toestemming is verleend. De landelijke dekking van de DBIR kan worden gecontroleerd middels gegevens vanuit de Inspectie voor de Gezondheidszorg. In het eerste volledige registratiejaar (2016) bedroeg de participatie 95% voor ziekenhuizen en 78% voor privéklinieken.

In **hoofdstuk 7** geven we een overzicht van de eerste uitkomsten van de DBIR-registratie. Van 2015 tot 2017 zijn 15.049 patiënten en 30.541 borstimplantaten geregistreerd. Volgens onze gegevens bedraagt de minimale incidentie in 2017 in Nederland: 1

implantaat per 1691 vrouwen. Het merendeel van de implantaten (85.2%) zijn geïmplanteerd vanwege cosmetische reden en 14,8% vanwege een borstreconstructie. Zowel de patiënt- als implantaatkenmerken verschillen significant per indicatiegroep. Patiënten die kiezen voor een borstvergroting zijn aanzienlijk jonger dan patiënten met een wens tot een borstreconstructie (31,5 versus 49,7 jaar). Voor beide indicaties was er in een jaar tijd (2016-2017) een duidelijke afname zichtbaar in het gebruik van getextureerde implantaten. Verder is in de reconstructieve groep een duidelijk toename in het gebruik van ronde en met siliconen gevulde implantaten opmerkelijk. Deze trend lijkt samen te vallen met de recente ophef rondom ALCL.

Een andere opvallende bevinding is de variatie tussen ziekenhuizen in de getroffen maatregelen ter infectiebestrijding. In het algemeen wordt een toename gezien in het gebruik van profylactisch intraveneus antibiotica, het aantal handschoenwissels vóór het inbrengen van het implantaat en in het spoelen van het implantaat met een antiseptische oplossing. Het gebruik van drains daalde in de reconstructieve groep maar nam toe in de cosmetische groep. Gegevens op langer termijn zullen antwoord gaan geven op de vraag of deze antiseptische voorzorgsmaatregelen en andere intraoperatieve technieken daadwerkelijke effect hebben op het risico op complicaties.

In het laatste hoofdstuk van dit proefschrift, **hoofdstuk 8**, beschrijven we een van de projecten uitgevoerd door 'the International Collaboration of Breast Registry Activities (ICOBRA)'. ICOBRA is een internationale multidisciplinaire werkgroep met expertise op het gebied van borstimplantaat-registraties. Zowel plastisch chirurgen, chirurgen, patiëntenverenigingen, regelgevende instanties en statistici zijn in deze werkgroep betrokken. Het doel van het project was om een gestandaardiseerde minimale dataset te definiëren ten behoeve van kwaliteitsmonitoring van borstimplantaatchirurgie wereldwijd. Als uitgangspunt werden de datasets van de huidige zes registraties vergeleken. Vervolgens werd een Delphi-procedure gestart waarbij elk panellid verplicht het belang van elk datapunt beoordeelde. Na vier delphi-rondes werd er consensus bereikt over een lijst van 32 datapunten. Datapunten waarover geen consensus werd bereikt (N=16), werden niet in de minimale dataset opgenomen en als 'optionele dataset' bestempeld. Ook werd er consensus bereikt over de definities van alle datapunten, waarbij de definities van de Australische dataset als uitgangspunt zijn gehanteerd. De ICOBRA-dataset is vrijwel volledig geïntegreerd in de DBIR-dataset. Naar verwachting

zal binnen twee jaar de set in alle huidige (en nog op te starten) borstimplantaatregistraties worden gebruikt binnen het ICOBRA-netwerk (Australië, Oostenrijk, Canada, Frankrijk, Duitsland, Ierland, Italië, Nederland, Nieuw-Zeeland, Zuid-Afrika, het Verenigd Koninkrijk en de Verenigde Staten). Het doel van deze gestandaardiseerde set is dat gegevens over borstimplantaten wereldwijd kunnen worden gekoppeld, waardoor er een actieve surveillance ontstaat. Problemen rondom implantaten komen zo sneller aan het licht. Ook kunnen de gegevens gebruikt worden voor een internationale benchmark op het gebied van borstimplantaatchirurgie.

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CURRICULUM VITAE

Pauline Spronk was born on the 6th of April 1988 in Tilburg, the Netherlands. At a younger age, she was convinced she wanted to become an actress. At the age of 12, she attended a special musical department at the Willem II college in Tilburg to pursue her interest in theatre through various extracurricular activities including drama and singing lessons.

Although she has always continued these activities, she became interested in biology during high school. In 2007, she started studying medicine at the Erasmus Medical Center in Rotterdam. During her studies, she worked as allocation coordinator for the Eurotransplant International Foundation.

Her first scientific project was named 'Diagnosis and treatment of lymph node metastases in pediatric rhabodomyosarcoma in the Netherlands', and was supervised by drs. C.E. Terwisscha van Scheltinga and Prof. R.M. Wijnen of the department of pediatric surgery in Rotterdam, in 2011. Thereafter, she got the opportunity to attend an extra surgical internship at the University of Heidelberg, in Germany, which she combined with a research project on 'Quality of life after a total pancreatectomy versus a Whipple procedure', supervised by Prof. J. Werner and Prof. M.W. Büchler. Her keen interest in science and surgery was awakened.

After graduating from medical school at the University of Leiden in 2014, she enrolled in a fulltime PhD program at the Dutch Institute for Clinical Auditing (DICA) under supervision of Prof. R.A.E.M. Tollenaar, dr. C.H. Smorenburg and dr. M.T.F.D. Vrancken Peeters, which has led to this thesis. During this three-year period, she combined the daily management of multiple national audits, especially the Nabon Breast Cancer Audit (NBCA) and the start-up of the Dutch Breast Implant Registry (DBIR), with scientific research on 'Quality of Healthcare', a hot topic in this current era of increasing transparency and accountability throughout our society.

From 2016 to 2018, she was actively involved in the International Collaboration of Breast Device Registries (ICOBRA), eleven contributing countries and organizations,

aiming to standardize global data in order to reflect global best practice and increase patient safety in breast implant surgery.

Pauline obtained clinical experience as a resident not in training at the department of Surgery at Spaarne Gasthuis in Haarlem/Hoofddorp and at the department of Plastic and Reconstructive Surgery at the Erasmus Medical Center in Rotterdam. Currently, she is working at the department of Surgery at Alrijne Ziekenhuis, in Leiderdorp.

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